TRANSIENT AND INTERMITTENT SYSTOLIC MURMURS IN NEWBORN INFANTS

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A PÆDIATRICIAN is often called upon to assess the significance of a systolic cardiac murmur in a newborn infant. When the murmur is associated with cardiac failure, cardiac enlargement, or central cyanosis, the diagnosis of congenital heart-disease is evident. More often these are absent and the diagnosis is established only after continued observation, when either the murmur disappears or signs of congenital heart-disease become manifest.

In this paper we report a follow-up study of newborn infants with systolic murmurs. In addition, maternal and perinatal factors were examined for any relation to the incidence of these murmurs.

Patients and Method of Study

111 newborn infants were found to have systolic murmurs in University College Obstetric Hospital between Jan. 1, 1948, and Jan. 1, 1957, during which time there were 11,855 live births. The observed prevalence of these murmurs was, therefore, 9·4 per 1000 live births.

Routine examination of normal infants born at term was carried out by the pædiatric house-physician on the first day of life, and again on the ninth day. Examinations were made more often if progress was unsatisfactory, and also in premature babies who remained in hospital until their weight was 2500 g. (5½ lb.) When murmurs were heard, confirmation was obtained in each case by the registrar, first assistant, or consultant to the children's department. We have found this routine practicable in an obstetric hospital having 1200–1400 live births annually, but it is subject to considerable observer error, depending as it does on the acuity of hearing and keenness of newly qualified housemen who change every six months. It is unlikely that skilled observers will be able to afford the time for these routine examinations in current obstetric-hospital practice. Our results must be interpreted with this clearly in mind. Chest X-rays were taken in the newborn period in 55 (50%) infants and electrocardiograms (E.C.G.s) in 42 (38%). At follow-up clinical, radiological, and electrocardiographic examinations were done as often as indicated. The age at death or at the last examination performed by one of us is shown in table I. It will be seen that 87% of the infants with transient systolic murmurs were kept under observation for over two years.

At follow-up patients were classified into one of four groups:

Group 1.—Congenital heart-disease.

Group 2.—Systolic murmurs, grade-2 intensity (Levine and Harvey 1949) or louder without other clinical, radiological, or electrocardiographic, signs of heart-disease.

Group 3.—Systolic murmurs of grade-1 intensity which were probably of no significance.

Group 4.—No murmurs.

Maternal, obstetric, and perinatal factors were analysed in relation to these four groups.

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TABLE I—DURATION OF FOLLOW-UP OR AGE AT DEATH

Age at follow-up or death (yr.)	Total	Congenital heart disease		Innocent murmurs		No murmur at follow-up
		Alive	Dead	Grade 2 or louder	Grade 1	
0–1	19	1 (4%)	15 (83%)	0	0	1 (2%)
1–2	21	3 (12%)	2 (11%)	1 (25%)	3 (27%)	6† (11%)
2–4	38	12 (48%)	1 (5%)	1 (25%)	6 (53%)	26 (49%)
4–6	18	3 (12%)	0	1 (25%)	1 (9%)	13 (25%)
More than 6	15	6 (24%)	0	1 (25%)	1 (9%)	7 (13%)
Total	111	25	18	4	11	53

† 1 child, a mongol, whose systolic murmur was last heard at 8 months of age, died of bronchopneumonia at 19 months. Necropsy showed a normal heart.

Results

At follow-up, the number of patients assigned to each of the groups was as follows:

Group 1.—43 children (39%) had congenital heart-disease (table II); 18 of these had died of an acute cardiac illness. The diagnosis was confirmed at necropsy in 16 cases and at thoracotomy in 1 other. The remaining child died at home, and post-mortem examination was not carried out; but central cyanosis with radiological evidence of cardiac enlargement, increased pulmonary vascularity, and dextrocardia with situs inversus left no doubt as to the diagnosis of congenital heart-disease.

TABLE II—FREQUENCY OF CONGENITAL CARDIAC MALFORMATIONS IN NEWBORN INFANTS WITH SYSTOLIC MURMURS

Type of malformation	Alive	Dead‡	Total
Ventricular septal defect	7	3	10
Atrial septal defect	2	3	5
Pulmonary stenosis or atresia	7	2	9
Aortic stenosis or atresia	5	0	5
Patent ductus arteriosus	0	4	4
Coarctation of the aorta	1	0	1
Tetralogy of Fallot	3	1	4
Transposition of the great vessels	0	3	3
Tricuspid stenosis	0	1	1
Persistent truncus arteriosus	0	1	1
Totals	25	18	43

‡ The major malformation is given in each case. Minor or physiologically unimportant additional cardiac defects occurred in 6 of the fatal cases.

25 children, surviving at the time of follow-up, had congenital heart-disease. The diagnosis was confirmed by cardiac catheterisation in 4 and by thoracotomy in 2 others. In the remaining 19 the diagnosis was established clinically and was supported by radiological and electrocardiographic studies.

Group 2.—At follow-up, 4 (4%) children had murmurs of grade-2 intensity or louder, but no other evidence of abnormality in the cardiovascular system.

Group 3.—11 (10%) children had soft (grade 1) murmurs as the only abnormality. In 3 of these the murmur had disappeared but later returned.

Group 4.—53 (48%) children had no murmur or other cardiovascular abnormality at follow-up examination. Most of these infants had no murmur after the first few weeks of life (table III). Thus 32 (59%) had no murmur by 2 weeks of age, and 47 (89%) by three months. Only 6 infants lost their murmur after 3 months of age.

Congenital heart-disease was confirmed in the neonatal period in all 18 fatal cases. At this time 10 had central

TABLE III—AGE AT WHICH SYSTOLIC MURMURS WERE LAST HEARD IN 53 INFANTS WITH NO MURMUR AT FOLLOW-UP

Age at which murmur was last heard (mos.)	No. of infants
0–3	47*
3–6	3
6–12	2
12–24	1
Total	53

* The murmurs were last heard during the first 2 weeks in 32.

cyanosis, 3 diastolic murmurs, 12 abnormal chest X-rays, and 7 abnormal E.C.G.s. In the neonatal period, however, there was no confirmatory clinical, radiological, or electrocardiographic evidence of organic heart-disease in 12 of the 25 children with congenital heart-disease surviving at the time of follow-up. Moreover, in 7 of these the murmur disappeared but later returned. Because these patients show the intermittence of some organic systolic murmurs they will be described more fully.

Case-reports

Case 1: *Pulmonary stenosis confirmed by cardiac catheterisation.*—A boy, birth-weight 4520 g. (10 lb.), born at thirty-nine weeks after a normal pregnancy and delivery. Rhythmic respiration was established within ten seconds, but several periods of apnœa took place after a few minutes. No murmur was heard at birth or at five hours, but a grade-2 systolic murmur was heard down the left sternal border at eight hours. The murmur was again heard on the sixth and eighth days but had disappeared by the fourteenth day, and was not present on the nineteenth or twenty-fourth days. It had returned by the ninth week and persisted.

Case 2: *Tetralogy of Fallot with pulmonary atresia confirmed at operation.*—A boy, birth-weight 3720 g. (8 lb. 3 oz.), born at thirty-eight weeks after normal pregnancy and delivery. A grade-1 murmur was heard on the ninth day of life but not heard five days later or on the twenty-second, twenty-ninth, or forty-second days, though during this time he became slightly cyanosed. The murmur returned on the forty-ninth day and persisted.

Case 3: *Turner's syndrome with coarctation of the aorta corrected surgically.*—A girl, birth-weight 3799 g. (8 lb. 6 oz.), born at thirty-seven weeks. The pregnancy was complicated by hydramnios, which was tapped three times. Delivery was by cæsarean section because of contracted pelvis. Regular respiration was established at birth, but there was a cyanotic attack which was thought to have resulted from inhalation of liquor amnii. A systolic murmur was heard at the apex two minutes after birth, but its intensity diminished after ten minutes. The murmur could not be heard on the fourth day, but it returned on the next day. There was no murmur on the seventeenth day, but a rough systolic murmur was heard again on the twenty-eighth day. It was heard at subsequent visits apart from one occasion at the third month.

Case 4: *Atrial septal defect, diagnosed clinically at follow-up examination. The chest X-ray showed a large pulmonary artery and increased pulmonary vascular markings, and the E.C.G. incomplete right bundle-branch block.*—A boy, birth-weight 3350 g. (7 lb. 6 oz.), born at thirty-nine weeks after a normal pregnancy and delivery. Rhythmic respiration was established at birth. A systolic murmur was heard on the first day, but not on the third or ninth. A grade-3 systolic murmur was present at 3 years.

Case 5: *Ventricular septal defect diagnosed clinically at follow-up examination. The chest X-ray showed bilateral cardiac enlargement and the E.C.G. left axis deviation with left-ventricular preponderance.*—A girl, birth-weight 3848 g. (8 lb. 8 oz.), born at forty weeks. The mother had compensated mitral stenosis, but the pregnancy and delivery were normal. Regular respiration was established at birth, though the infant remained irritable and was cyanosed during the first day of life. A grade-2 systolic murmur was heard at seven hours but had disappeared by the seventh day and was not heard again until follow-up examination at 3 years of age, when there was a grade-3 systolic murmur, loudest at the left sternal border at the level of the fourth costal cartilage.

Case 6: *Ventricular septal defect diagnosed clinically at follow-up examination. The chest X-ray showed both left and right ventricular enlargement and the E.C.G. left-ventricular preponderance.*—A boy, birth-weight 2880 g. (6 lb. 5 oz), born at thirty-seven weeks after a normal pregnancy. The membranes ruptured spontaneously forty-five hours before delivery. Forceps were applied because of slow progress after a second stage of one and a half hours. The umbilical cord was twisted once round the neck of the infant. He gasped thirty seconds after delivery, but regular respiration was not established for five minutes. There was no murmur at birth but on the ninth day a grade-2 systolic murmur was heard at the left sternal border at the level of the fourth intercostal space. There was no cyanosis or other abnormality. The chest X-ray and E.C.G. were within normal limits. The murmur diminished in intensity, and could not be heard by the sixteenth day. At follow-up examination at 11 months of age the boy had a grade-3 systolic murmur, loudest at the left sternal border at the level of the fourth intercostal space.

Case 7: *Aortic stenosis diagnosed clinically at follow-up examination. The chest X-ray showed moderate cardiac enlargement and the E.C.G. left-ventricular preponderance.*—A boy, birth-weight 3950 g. (8 lb. 12 oz.), born at forty-one weeks after a normal pregnancy and delivery. He gasped immediately at birth, but regular respiration was not established for seven minutes. A grade-4 systolic murmur was heard, loudest just medial to the apex during the first 12 hours, but had disappeared at 24 hours, and was not present at 6 days or 6 months. When re-examined at 4 years and 7 months he had a grade-3 systolic murmur, consistent with aortic stenosis.

The age at which the murmur was first heard, its intensity, and its site were of no value in diagnosis.

Table IV shows that systolic murmurs were first heard during the first week of life in 51% of infants with congenital heart-disease and 58% of infants with transient systolic murmurs. Loud murmurs of grade-3 or greater intensity were heard in 46% of infants both with congenital heart-disease and with transient systolic murmurs. Diastolic murmurs were present in 4 infants, 1 of whom was found at follow-up examination to have a normal heart. The remaining 3 died, and the presence of a large patent ductus arteriosus was confirmed at thoracotomy in 2 and at necropsy in the 3rd. Associated congenital abnormalities occurred more often in infants with congenital heart-disease, in whom they were found in 26% (11 out of 43),

TABLE IV—CHARACTERISTICS OF MURMUR DURING THE NEONATAL PERIOD RELATED TO FINDINGS AT FOLLOW-UP

Clinical features of murmur	Total	Congenital heart-disease	Innocent murmurs		No murmur at follow-up
			Grade 2 or louder	Grade 1	
Day first heard:					
0–1	46	15 (35%)	2 (50%)	4 (36%)	25 (47%)
2–7	14	7 (16%)	0	1 (9%)	6 (11%)
8–14	36	16(37%)	2 (50%)	4 (36%)	14 (26%)
over 14	15	5 (12%)	0	2 (18%)	8 (15%)
Intensity:					
1	4	3 (7%)	0	0	1 (2%)
2	56	20 (47%)	2 (50%)	6 (55%)	28 (53%)
3	21	7 (16%)	0	2 (18%)	12 (23%)
4	10	4 (9%)	1 (25%)	1 (9%)	4 (8%)
5	20	9 (21%)	1 (25%)	2 (18%)	8 (15%)
6	0	0	0	0	0
Site of greatest intensity:					
Apex	34	10 (23%)	2 (50%)	2 (18%)	20 (38%)
L.S.B.	47	16 (37%)	2 (50%)	4 (36%)	25 (36%)
Precordial ..	17	10 (23%)	0	4 (36%)	3 (6%)
Base	13	7 (16%)	0	1 (9%)	5 (9%)

L.S.B. = left sternal border.

than in those with transient murmurs in whom they were found in only 6% (3 out of 53). There were 2 mongols in the total of 111 infants with murmurs. Neither had congenital heart-disease. Delayed onset of respiration, respiratory distress, and cerebral irritation were not related to the significance of the murmurs.

Chest X-rays in the newborn period were valuable in confirming the diagnosis of congenital heart-disease, but were sometimes difficult to interpret. Cardiac enlargement and abnormal pulmonary vascular markings were found in 83% (20 out of 24) of newborn infants with congenital heart-disease. Radiological abnormalities, however, were also suspected in 45% (10 out of 22) of infants without heart-disease, but could not be confirmed because of the difficulty in interpreting pulmonary vascular markings and heart size in radiograms not taken in full inspiration. The diagnosis of the 4 infants with congenital heart-disease who had normal chest X-rays in the neonatal period was pulmonary stenosis in 3 and ventricular septal defect in the 4th. Abnormalities in the E.C.G., such as left or excessive right-ventricular preponderance, were often

TABLE V—BIRTH-WEIGHTS

Weight (g.)	Total	Congenital heart-disease	Innocent murmurs		No murmur at follow-up
			Grade 2 or louder	Grade 1	
1001–1500	2	2 (5%)	0	0	0
1501–2000	3	2 (5%)	0	0	1 (2%)
2001–2500	6	2 (5%)	0	0	4 (8%)
2501–3000	25	15 (35%)	0	3 (27%)	7 (13%)
3001–3500	28	6 (14%)	1 (25%)	4 (36%)	17 (31%)
3501–4000	34	12 (28%)	2 (50%)	4 (36%)	16 (32%)
4001–4500	11	3 (7%)	1 (25%)	0	7 (13%)
4501–5000	2	1 (2%)	0	0	1 (2%)
Totals ..	111	43	4	11	53

diagnostic but were sometimes equivocal. Abnormal records were obtained in 65% (11 out of 17) of infants with congenital heart-disease, but were also suspected in 16% (4 out of 25) of infants without heart-disease because of the difficulty in assessing an abnormal degree of right-ventricular preponderance in the neonate. Of the 6 infants with congenital heart-disease whose E.C.G.s were within normal limits, 2 had pulmonary stenosis, 2 ventricular septal defects, 1 aortic stenosis, and the 6th, a persistent truncus ateriosus.

Abnormalities of pregnancy, such as toxæmia or antepartum hæmorrhage, mother's age at delivery, a family history of congenital malformations, or the length of gestation, were not related to the status at follow-up. Neither the method nor the duration of delivery nor the presence of fœtal distress had any relation to the significance of the murmurs.

Birth-weights of infants with congenital heart-disease were lower than those with transient systolic murmurs (table V). Of children with congenital heart-disease, 50% (21) had birth-weights under 3000 g. (7 lb.) as compared with only 23% (12) with transient murmurs. The corresponding proportions under 2000 g. (4 lb. 6 oz.) were 15% (6) and 2% (1).

Transient systolic murmurs were commoner in girls than boys (table VI); thus, of 53 children whose murmurs disappeared, 62% were girls, though in children with congenital heart-disease the sex-distribution was equal.

TABLE VI—SEX-DISTRIBUTION

Sex	Totals	Congenital heart-disease	Innocent murmurs		No. murmur at follow-up
			Grade 2 or louder	Grade 1	
Male ..	51 (46%)	22 (50%)	3 (75%)	6 (55%)	20 (38%)
Female ..	60 (54%)	21 (50%)	1 (25%)	5 (45%)	33 (62%)
Totals ..	111	43	4	11	53

Discussion

Estimates of the frequency of systolic murmurs in newborn infants have varied from 0·5% (Gyllensward 1956) to 38% (Creery 1953). This considerable variation is related to the frequency with which auscultation was performed (Siemsen 1938) and to the intensity of murmurs accepted as significant. Taylor (1953), who found a prevalence of 4·8%, included only murmurs of grade-2 intensity or louder, while Burnard (1958) reported murmurs in 37% of infants investigated by careful auscultation and phonocardiographic studies during the first 11 hours of life. Other observers have found a prevalence of 25% (Siemsen 1938), 1·9% (Lyon et al. 1940), and 1·7% (Richards et al. 1955). In our series, systolic murmurs were heard in 0·94%. This low prevalence is partly due to an observer error. House-physicians with a special interest in cardiovascular disease found a significantly higher proportion of infants with murmurs.

The prevalence of persistent murmurs has been estimated as 16% (Lyon et al. 1940), 15% (Taylor 1953), 57% (Creery 1953), and 24% (Gyllensward 1956).

Richards et al. (1955) found that a systolic murmur at birth carried a probability of congenital heart-disease of 1 in 12. If the murmur was heard again at 6 months the probability was 1 in 3, and, if it persisted to 12 months, 3 in 5. These workers kept their infants under observation for twelve months and, in view of the difficulty sometimes experienced in making the diagnosis of congenital heart-disease at this age, the true prevalence of heart-disease was probably higher. In our series of infants with systolic murmurs in the neonatal period, 40 of the 93 surviving at follow-up had persistent murmurs. Of these, 25 had congenital heart-disease. In the total series, 39% had congenital heart-disease. Over a quarter (7 out of 25) of infants with congenital heart-disease surviving at the time of follow-up examination had intermittent murmurs during the first months or years of life, and the diagnosis was established by a long-term follow-up. Only 11% of infants with transient systolic murmurs lost their bruit after the 3rd month of life.

Few observations outside the cardiovascular system were found to aid in establishing the significance of systolic murmurs. Congenital heart-disease was found more often than transient murmurs in premature infants, and in those in whom other congenital malformations were present. Transient murmurs were found 1·7 times more often in girls than in boys. Analysis of other perinatal factors did not show any relation to the cause or significance of systolic murmurs. The greater prevalence of systolic murmurs in infants with anoxia, found by Burnard (1958), was not apparent in our series.

The cause of transient systolic murmurs in newborn infants is not known, but some theoretical considerations have been discussed by Leatham (1959). Murmurs are associated with closure of the ductus arteriosus in newborn lambs (Dawes et al. 1955). A left-to-right shunt through the ductus has been demonstrated for some days after birth in newborn infants (Adams and Lind 1957, James and Rowe 1957, Rowe and James 1957). Burnard (1958) has suggested that the transient murmurs in newborn infants may be due to flow through a patent ductus arteriosus.

The prevalence of congenital heart-disease has been estimated as 5 per 1000 (Keith et al. 1958). Among our infants with systolic murmurs detected in the neonatal period, the frequency of congenital heart-disease was 3·6 per 1000 total live births. The total prevalence, however, was higher as some children with congenital heart-disease did not have murmurs in the neonatal period.

Newborn infants with systolic murmurs should be kept under observation for a number of years because neither the disappearance of these murmurs, nor the absence of radiological or electrocardiographic abnormalities in the newborn period, rule out the diagnosis of congenital heart-disease.

Summary

111 of 11,855 newborn infants (0·94%) had systolic murmurs. 39% of these had congenital heart-disease. At follow-up, 14% had persistent murmurs which were probably innocent, and 48% had lost their murmur.

Systolic murmurs due to congenital heart-disease were found more often than innocent transient murmurs in premature infants and in those in whom other congenital malformations were present. Innocent transient systolic murmurs were found 1·7 times more frequently in girls than in boys.

Analysis of other perinatal factors did not show any relation to the significance of systolic murmurs.

Over a quarter of the infants with congenital heart-disease, surviving at the time of the follow-up, had intermittent murmurs during their first few months or years of life. Infants with systolic murmurs should be kept under observation for a number of years, because even the disappearance of the murmur does not exclude congenital heart-disease.

Our thanks are due to all the housemen and registrars who have examined the newborn at University College Hospital from 1948 to 1957.

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"... Why are so many symposia so devastatingly boring? ... Why has the symposium come to such a pass? It is my opinion that this has happened because symposia are being used for something other than for which they are eminently suited: the extension of knowledge. A rapidly increasing number of symposia are being held for the sole purpose of drug promotion ... I have no quarrel with honest advertising of drugs—outright advertising ... But an advertisement should be called an advertisement. An advertisement in a medical journal may not be presented as if it were part of the text. In the same way, a collection of biased promotional speeches for a drug must not be presented as if it were an unbiased educational forum. I take issue with all who are parties to this perversion of an important postgraduate educational instrument into an insidious promotional device. There is the real danger that, should the symposium continue to be degraded by this practice, good symposia will disappear."—Dr. WALTER MODELL, *Clin. Pharmacol. Ther.* 1960, **1**, 689.

THE METABOLIC EFFECTS OF ALDOSTERONE GIVEN BY MOUTH

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THE essential hormones of the adrenal cortex are hydrocortisone and aldosterone. For replacement therapy in Addison's disease and after total adrenalectomy, tablets of cortisone acetate and 9α-fluorohydrocortisone acetate (fludrocortisone) are used.

Studies have been made to see whether aldosterone instead of fludrocortisone can be given by mouth for maintenance of sodium balance in these patients. Two preparations were used: an aqueous solution of *d*-aldosterone (0·5 mg. per ml.) and tablets of 0·5 mg. *d*-aldosterone 21-monoacetate. The metabolic effects have been investigated in an adrenalectomised dog, a normal man, and two women who had had total adrenalectomy.

Methods

The adrenalectomised dog (body-weight 75 lb.) was maintained with 37·5 mg. cortisone acetate and 0·2 mg. fludrocortisone daily by mouth; food intake was constant (sodium 34 mEq., potassium 47 mEq. per day). Studies were made twenty-four hours after the last replacement therapy and 18 hours after the last meal. At the start of each study, 25 mg. cortisone was given by mouth, and 250 ml. physiological saline by stomach tube. The intragastric saline was repeated at two, four, and six hours. Urine was collected in thirty-minute periods for eight hours, and the sodium and potassium excretion measured. There was a two-hour control period before the steroid was given.

Two studies were made on the normal man. In the first, he took four-hourly identical feeds for four days; and on the fourth day a single dose of 3 mg. *d*-aldosterone in solution was given, urine was collected at intervals of two to four hours, and the sodium, potassium, and creatinine content was estimated. For the second study, he received a constant diet, the sodium, potassium, chloride, and nitrogen content of which was determined by analysis. Twenty-four-hour urine collections were made and the outputs of sodium, potassium, chloride, nitrogen, creatinine, 17-hydroxycorticosteroids, and 17-ketosteroids were measured. After equilibration, there were two control days, two days on which 5 mg. per day *d*-aldosterone monoacetate was given in divided doses, two days on 10 mg. per day, and two recovery days.

The adrenalectomised women were studied while receiving constant diets, and urine and fæces were collected. Patients were weighed and had blood-pressures recorded at a fixed time each day. Blood was taken twice weekly for plasma-electrolyte and blood-urea estimations and absolute eosinophil-counts.

Biochemical methods used were: (1) sodium and potassium by an 'E.E.L.' flame photometer; (2) urinary chloride by electrometric titration; (3) fæcal and diet chloride by Carius' digestion; (4) nitrogen by Kjeldahl digestion and nesslerisation; (5) creatinine by the alkaline-picrate method; and

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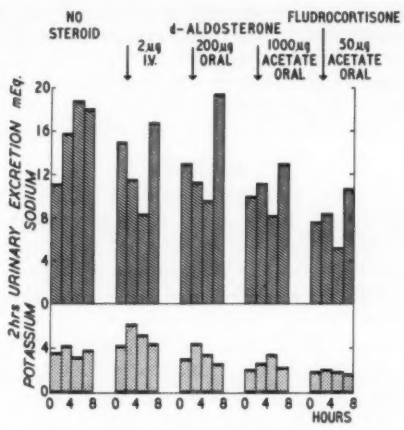

Fig. 1—Studies in an adrenalectomised dog.

250 ml. physiological saline given orally every 2 hours (0, 2, 4, and 6 hours). Urinary sodium and potassium excretion in each 2-hour period is shown. Changes produced by administering at 2 hours 2 µg. *d*-aldosterone intravenously, 200 µg. *d*-aldosterone in solution by mouth, 1000 µg. *d*-aldosterone monoacetate in tablets, or 50 µg. fludrocortisone acetate as a tablet, are compared with urinary electrolyte excretion in a study in which saline was given but no steroid.

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(6) urinary steroids by the methods usually used in this laboratory (Moxham and Nabarro 1956). Urinary aldosterone was determined by a method based on that of Ayres et al. (1957).

Results

Adrenalectomised Dog

Fig. 1 shows the results of studies with the adrenalectomised dog. 2 µg. *d*-aldosterone given intravenously had a considerable effect on urinary sodium and potassium. 100 µg. *d*-aldosterone in solution given by stomach tube produced little change; 200 µg. reduced the sodium excretion but did not increase potassium output as much as the 2 µg. intravenously. The tablets of *d*-aldosterone monoacetate were even less effective: 1 mg. was needed to produce a comparable effect on sodium excretion, and again, the increase in potassium output was small. Fig. 1 also shows the effect of 50 µg. fludrocortisone acetate. It had more effect than 1000 µg. *d*-aldosterone acetate on sodium excretion but rather less on urinary potassium output.

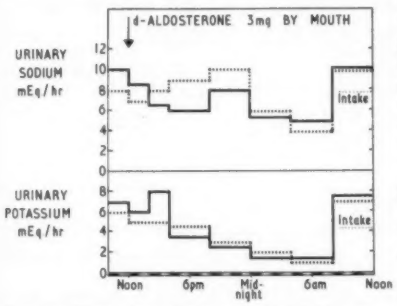

Fig. 2—Effect of a single oral dose of 3 mg. *d*-aldosterone in aqueous solution. Normal man on 4-hourly feeds of constant composition.

Mean of 2 control days—dotted line. Day of aldosterone administration—continuous line.

Normal Man

The results of giving 3 mg. *d*-aldosterone in solution to a normal man are shown in fig. 2. In the 12 hours after administration there was a modest reduction of urinary sodium and a slight increase of potassium. The urine in the twenty-four hours after the aldosterone was taken contained a trace of free steroid and 462 µg. of the acid-hydrolysable conjugate. Fig. 3 shows the results of giving 5 or 10 mg. monoacetate daily in divided doses. There was sodium retention—shown best by the increased output on the recovery days—and a gradual increase of potassium excretion with subsequent retention. There was no increase of urinary acid-hydrolysable aldosterone on the days when the monoacetate was being given. The urinary creatinine output did not show any consistent alteration; chloride excretion was parallel to that of sodium; nitrogen balance, urinary 17-hydroxycorticosteroid and 17-ketosteroid excretions were unchanged.

Patients after Adrenalectomy

Fig. 4 shows the results in the first adrenalectomised woman. Prednisone was used instead of cortisone to accentuate the electrolyte changes and, when prednisone 2·5 mg. was given every six hours, it was found that 0·3 mg. per day fludrocortisone was needed for the maintenance of sodium balance. When this was changed to 10 mg. per day *d*-aldosterone monoacetate, there was slight sodium retention and weight gain. The effect of two intramuscular doses of 1·0 mg. *dl*-aldosterone monoacetate in oil at twelve-hour intervals was comparable to that of 10 mg. *d*-aldosterone monoacetate given by mouth. The plasma electrolytes and blood-urea were normal throughout the study. Absolute eosinophil-counts were 84–160 per c.mm. and were not altered by the aldosterone. Urinary creatinine output and nitrogen balance were unchanged.

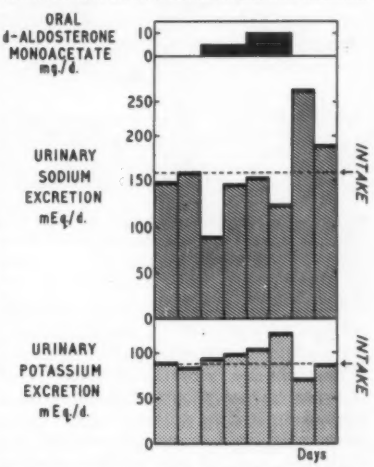

Fig. 3—Effect of *d*-aldosterone 21-monoacetate tablets on urinary sodium and potassium excretion. Aldosterone given in divided doses 6-hourly. Normal man.

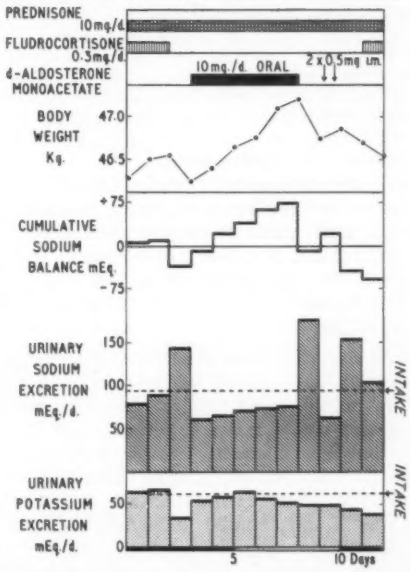

Fig. 4—Effect of tablets of *d*-aldosterone 21-monoacetate on bodyweight, sodium balance, and urinary sodium and potassium in an adrenalectomised woman taking prednisone.

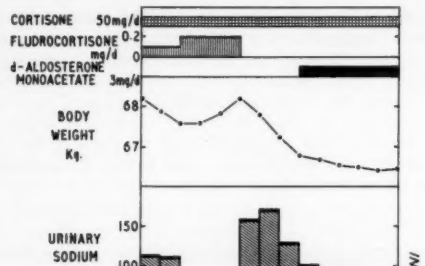

Fig. 5—Effect of tablets of *d*-aldosterone 21-monoacetate on body-weight, and urinary sodium and potassium in an adrenalectomised woman taking cortisone.

The second adrenalectomised patient was studied while taking 12·5 mg. cortisone six-hourly (fig. 5). Fludrocortisone 0·1 mg. per day allowed sodium loss; whereas with doses of 0·2 mg. per day there was retention. On this intake of sodium, it appeared that about 0·125 mg. fludrocortisone a day was needed for sodium balance, and balance was again achieved when 3 mg. *d*-aldosterone monoacetate was given. The urinary creatinine and nitrogen output were unaltered. Absolute eosinophil-counts ranged from 25 to 70 per c.mm., tending to increase while aldosterone was being given. Plasma electrolytes and blood-urea were normal when the patient entered hospital; during the pre-aldosterone period the plasma-sodium fell and plasma-potassium and blood-urea rose. At the end of the balance study the figures were: sodium 134 mEq. per litre, potassium 5·2 mEq. per litre, and urea 65 mg. per 100 ml. Subsequently the patient was maintained with cortisone 12·5 mg. six-hourly and *d*-aldosterone monoacetate 1 mg. eight-hourly. After one week the figures were: sodium 142 mEq. per litre, potassium 5·1 mEq. per litre, and blood-urea 27 mg. per 100 ml. This replacement therapy has been continued for a further two months; and general health, body-weight, blood-pressure, and biochemical tests have remained satisfactory. Before this study the patient had been receiving the same dose (12·5 mg. every six hours) of cortisone and 0·1 mg. fludrocortisone a day.

Discussion

Kekwick and Pawan (1954) found that 100 μg. aldosterone given daily by mouth maintained sodium balance in a patient with Addison's disease. Thorn et al. (1955) gave 1 mg. per day of aldosterone by mouth to a patient with normal adrenals, and to one with Addison's disease. They were unable to show any change in sodium or potassium excretion.

Our studies with the adrenalectomised dog suggest that little of the aldosterone given by mouth reaches the kidneys in physiologically active form. In the normal subject absorption of free aldosterone given in solution seems to have been adequate, but it was converted to the inactive acid-hydrolysable conjugate before it reached the renal tubules. The 21-monoacetate is either poorly absorbed or is metabolised differently from the free steroid; if sufficient is given, however, a mineralcorticoid action can be shown. In the adrenalectomised subjects, aldosterone by mouth had 1/25th to 1/30th the potency of fludrocortisone in the maintenance of sodium balance. These studies have been made in only a few subjects, and the absorption and metabolism of aldosterone 21-monoacetate may well vary from person to person. At present aldosterone by mouth seems unlikely to replace fludrocortisone in the maintenance therapy of patients either with Addison's disease or after total adrenalectomy.

Summary

Studies of the metabolic effects of aldosterone given orally have been made in an adrenalectomised dog, a normal man, and two women who had had total adrenalectomy performed. The preparations used were *d*-aldosterone in aqueous solution and tablets of *d*-aldosterone 21-monoacetate.

Aldosterone in solution was well absorbed but was quickly converted to a physiologically inactive conjugate. In the dog, the 21-monoacetate was less effective than the free aldosterone, but in the adrenalectomised women it was effective in maintaining sodium balance. About 3 mg. a day of aldosterone monoacetate given orally was needed to replace 0·1 mg. fludrocortisone.

We wish to thank Dr. A. K. Pittman, of Ciba Laboratories, Ltd., Horsham, for supplies of aldosterone; the staff of the Courtauld Institute of Biochemistry for the blood and plasma analyses; the ward sisters, nurses, and dietitians for their invaluable help; Miss E. D. Hewland for the figures; and the clinical reseach committee of the Middlesex Hospital for the provision of laboratory facilities. The aldosterone estimations were made in connection with a project sponsored by the Medical Research Council.

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THYROID FUNCTION IN THE PRESENCE OF BREAST CANCER

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SINCE Beatson (1896) reported that a patient with metastatic breast cancer improved after castration and the administration of thyroid extract, considerable attention has been paid to endocrine/breast-cancer relations.

Results reported by Edelstyn et al. (1958) suggested that patients with disseminated breast cancer have a lower level of thyroid function than those with localised disease. Confirmation of these results would open up a new field of endocrine/cancer relations and would be of great value in the clinical study of patients treated for breast cancer. Measurement of thyroid function at the time the patient first reported with breast cancer, and at regular intervals thereafter, would then assist in the detection of subclinical metastatic spread through the vascular tree and might, in turn, allow earlier treatment for disseminated disease.

* Working under a grant from the State Cancer Council of New South Wales.

High levels of protein-bound iodine have been reported by Carter et al. (1960) in patients with disseminated breast cancer.

Because of the importance of the report of Edelstyn et al. (1958), we set out to confirm their results in our breast and thyroid clinics.

Methods

The thyroidal radioiodine uptake-rate (k_1) was measured by the method of Oddie et al. (1955). This accurate measurement involves a correction for the patient's extrathyroidal iodine space in the neck tissues and makes allowance for the effect on uptake of the renal excretion-rate. The logarithm of the uptake-rate is known to be normally distributed for both euthyroid and hyperthyroid patients, and, using this parameter, a careful statistical analysis has shown significant changes in the mean euthyroidal function with age, sex, goitre size, and pre-menopausal or postmenopausal state (Oddie et al. 1960).

The classification of cases of primary cancer of the breast followed the principles set out by Portmann (1943):

Stage I: tumour movable and localised to breast tissue; no evidence of skin or other tissue involvement.

Stage II: as (I) but with axillary lymph-nodes involved.

Stage III: diffuse infiltration of breast with fixation to chest wall; skin ulceration with tumour; involvement of axillary lymph-nodes; but no distant metastasis.

Stage IV: as stages I, II, or III, but with clinical or radiographic evidence of widespread metastasis.

Results

Of 62 radioiodine-uptake studies performed, 29 were on patients with stage-I carcinoma, 11 with stage II, 3 with stage III, and 19 with stage IV or definite evidence of blood-borne metastasis.

The mean log. 10^3k_1 for each group, and the associated standard errors, are shown in the accompanying table.

There is no significant difference between the means of groups I, II, and III, nor does the combined mean differ

STAGE OF CANCER AND RADIOIODINE UPTAKE

Stage	No. of cases	Log. 10^3k_1 (mean)	S.E. of mean
I	29	0·444	0·035
II	11	0·351	0·092
III	3	0·056	0·218
I, II, and III combined ..	43	0·393	0·037
IV	19	0·336	0·053

significantly from that of group IV; a *t*-test of significance gave $0{\cdot}30 < P < 0{\cdot}40$.

In an attempt to eliminate the variation due to age, menopausal state, or the presence of goitre not related to the patient's mammary cancer, the logarithm of the ratio of each patient's thyroidal uptake-rate to the expected mean euthyroidal rate (Oddie et al. 1960) was determined and the analysis repeated. Again no significant differences were found; a *t*-test of the group-IV mean against the combined mean of groups I, II, and III gave $0{\cdot}80 < P < 0{\cdot}90$.

Finally, using each patient's measured thyroid uptake-rate (k_1), renal excretion-rate (k_2), and the neck-tissue correction, the 24-hour neck fraction was calculated using the formula of Oddie et al. (1955). This was the quantity measured by Edelstyn et al. (1958). If a significant difference had been found in these figures, we would then have looked for a difference in the renal function or in the behaviour of the iodine space between patients with or without blood-borne metastases. No difference, however, was observed; the group-IV mean was 0·52, and that of groups I, II, and III combined was lower at 0·49.

Furthermore, in 5 patients whose thyroidal uptake-rates were measured as their disease progressed from stages I or II to stage IV, no significant change in uptake-rate was observed.

Discussion

Using groups of patients, presumably similar to those reported by Edelstyn et al. (1958), we have not been able to show any difference in thyroid function between patients with local disease or with blood-borne metastases from carcinoma of the breast.

In view of this finding, we undertook to study the data of Edelstyn et al. (1958) statistically, assuming their data on percentage uptakes in the neck to be percentage uptakes in the thyroid gland (a reasonable approximation at 24 hours), assuming average renal clearance-rates, and converting the percentage uptakes to thyroidal uptake-rates (k_1). An analysis of the rates showed that the means differed highly significantly with $P < 0{\cdot}001$. Thus the data published by these workers yield their original conclusion when analysed by our methods.

We think, on the other hand, that the study reported here presents a more direct approach to the precise measurement of thyroid function. The introduction of tracer doses intravenously avoids any effects of the possible impairment of their absorption by the gastric mucosa, particularly in patients with far-advanced disease. The T-test of Fraser, also reported by Edelstyn et al. (1958), is an indirect method of measuring thyroid function and may therefore be affected by other variables such as poor renal excretion, poor fluid-intake, or failure to collect the total output of urine. In any one test, only one measurement of thyroid function was made in our study, and this measurement is known to be accurate to better than 5% from tests on standard manikins supplied by the Oak Ridge Institute of Nuclear Studies (ORINS) (Brucer 1957).

Edelstyn et al. (1958) felt that widespread cancer might affect thyroid function: " Metastases in the pituitary or in the thyroid or in both may destroy functioning tissue." A patient in the present series with stage-IV disease and metastatic deposits in the posterior pituitary and hypothalmus, and with diabetes insipidus had normal thyroid function.

It seems to us that the results of Edelstyn et al. (1958) and those from this unit are in conflict, but the alternative explanation that patients with disseminated disease have a normal uptake of iodine (this report), a lowered neck content at times later than 1 hour (Edelstyn et al. 1958), and an associated raised serum protein-bound iodine (Carter et al. 1960) might be worth investigating.

Summary

Using an accurate method of measuring thyroid function in cases of breast cancer, no difference from normal was found in those with local disease or in those with metastasis.

The work was supported by a generous donation from the Northbridge Auxiliary of the Royal North Shore Hospital of Sydney. We wish to thank Dr. G. A. Edelstyn for supplying all his data for reanalysis.

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AN ISOPRECIPITATION REACTION DISTINGUISHING HUMAN SERUM-PROTEIN TYPES

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DURING the past decade it has become apparent that human beings differ in their serum-proteins as well as in their red blood-cells. Genetically controlled variations have been described in haptoglobins and transferrins (Smithies and Connell 1959), γ-globulins (Grubb 1957, Ropartz 1960), and in the Gc system definable by immunoelectrophoresis (Hirschfeld and Beckman 1960). Though the chemical differences between the alternative proteins are not yet known, they are generally assumed to be small —analogous to the single aminoacid substitutions that distinguish the different human hæmoglobin half-molecules (Hunt and Ingram 1959) and the small sugar substitutions that distinguish the blood-group substances (Morgan 1959). Nevertheless, the possibility remains that these or other serum-proteins are sufficiently different in structure to induce serum-protein isoimmunisation when blood is transfused.

Such a reaction is already known in rabbits. Oudin (1956), Dray and Young (1959), and others have shown that rabbits can be immunised with serum from other rabbits of different γ-globulin type. In the original experiments the foreign plasma was introduced with adjuvants, but recent observations (S. Dray, personal communication) have shown that adjuvants are unnecessary for immunisation. Three or four intravenous injections of serum from rabbits of another γ-globulin type led to the production in recipients of well-defined precipitating antibodies.

The experiments described here were undertaken to find out whether any similar reaction can be shown in man. Sera were obtained from subjects who had received multiple transfusions and were tested for precipitating antibodies against a panel of sera chosen to represent all the available genetically controlled serum-protein types. A serum has been found which gives strong precipitation with some, but not all, sera; and this reaction defines a polymorphism involving the α_2-globulins. Besides being of genetic interest, this finding raises the possibility that serum-protein isoimmunisation takes place in man and represents a clinical problem in persons receiving blood-transfusions.

Materials and Methods

Post-transfusion sera.—These were obtained from patients at the Clinical Center of the National Institutes of Health, Bethesda, who had received 5 or more transfusions. The indications for transfusion included open-heart surgery, hæmolytic and aplastic anæmias, pelvic tumours, and leukæmias. Wherever possible, blood-samples were drawn between 10 and 30 days after the last transfusion. Sera were stored at −20°C and were tested within 5 days of collection. Many of the subjects had received 30 or more transfusions.

Panel sera.—These were selected from the collection of the Section on Geographic Medicine and Genetics of the National Institute of Arthritis and Metabolic Diseases. The 24 sera included haptoglobin types 1-1, 2-1, 2-2, 2-1M, and O; transferrin types CC, CD, and BC; and γ-globulin types Gm a+, Gm a−, Gm b+, Gm b−, Gm x+, and Gm x−. In addition, 3 sera from patients with definite rheumatoid arthritis having high titres of rheumatoid factor, and 1 serum from a patient with well-developed lupus erythematosus (L.E.) having positive L.E. histological preparations and high titres of antinuclear antibodies, were used. The sera had been stored at −20°C for periods varying from 2 days to 2 years. Storage did not alter the reaction to be described. The sera were from different population groups, including American whites (sixteen), American Negroes (three), Micronesians (three), an Alaskan Eskimo, and a Viet-Namese.

Gel-diffusion precipitation technique.—The Ouchterlony procedure was carried out in 5 cm. petri dishes containing 8 ml. of 0·9% 'Oxoid Ionagar' (w/v) in 0·07 *M* sodium phosphate buffer, pH 7·0, with 0·001 *M* sodium ethylenediaminetetra-acetate and 0·001 *M* sodium azide. With a die, six wells 6 mm. in diameter were cut round a centre well of the same size. The circumferences of the centre well and peripheral wells were 4 mm. apart. After removal of the agar cores from the wells, the bases of the latter were sealed with small volumes of molten agar. The post-transfusion sera were placed in the centre wells and panel sera in the peripheral wells. The plates were stored at room temperature and observed at 18 hours (by which time clear-cut precipitation was usually visible), 48 hours, and 4 days. The precipitation is best seen by oblique illumination from below against a dark background.

Immunoelectrophoresis.—This was done by the micromethod of Grabar and Williams (1955) and Scheidegger (1955) using standard lantern-slide plates coated with agar made up in barbitone buffer 0·01 *M*. pH 8·4. Antibody (or antigen) was placed in the side well and examined after reacting for 18 hours, by which time well-defined precipitates were visible. The reaction was continued to 36 hours, after which the plates were washed in saline and stained.

Starch-gel electrophoresis.—Starch gel (Connaught Laboratories, Toronto) was made up in *tris*-(hydroxymethl)-aminomethane buffer (Poulik 1957) and poured into 6 × 80 × 150 mm. trays. Samples were inserted as a starch paste (Smithies 1955) into a slot 3 mm. wide. Electrophoresis was carried out for 5 hours at 6V per cm. The position of the components was identified in a small strip of gel; the various components were eluted by the method of Gordon (1960) and were concentrated by ultrafiltration.

Preparation of γ-globulin components.—Separation of 7S and 19S γ-globulins was achieved by sucrose density-gradient centrifugation (Fudenberg and Kunkel 1957) using 40, 30, 20, and 10% solutions of sucrose.

Bentonite-flocculation test.—The method of Bozicevich et al. (1958) was used.

Latex-fixation test.—This was carried out as described by Singer and Plotz (1956), using the Hyland 'RA-test' kit (Hyland Laboratories, Los Angeles, California).

Observations

A precipitin was found in the serum of a patient who had received many transfusions. He had a long and varied history of illness.

The patient is a 64-year-old white American retired executive of Hungarian birth. At the age of 16 he had albuminuria which lasted for 4 years. In 1934, while still living in Budapest, he had an episode of sudden onset of paræsthesiæ and paralysis of the legs. This resolved spontaneously in 2 months. A second episode, involving complete paralysis up to the waist, weakness of the arms, and loss of sensation and reflexes in the legs, took place in the United States in 1958. Cerebrospinal fluid contained 73 mg. protein and 150 lymphocytes per ml. Polyneuritis of unknown cause was diagnosed, and again remission was spontaneous.

The patient also had symptoms of peptic ulceration dating from 1921, with gastrointestinal hæmorrhage in 1938 and 1940. In 1941 a gastroenterostomy was performed, but symptoms and hæmorrhage have recurred at intervals. The patient was again admitted to hospital in 1958, at which time he was reported to have low red-cell counts, low hæmoglobin levels, and high white-cell and platelet counts. X-ray examination suggested an ulcer crater in the proximal duodenum. The bleeding

continued for a month and then ceased, and with the help of blood-transfusions the hæmoglobin was raised to 14 g. per 100 ml. Because of the high white-cell count and the presence of numerous megakaryocytes in the bone-marrow and some in the peripheral blood, the possibility that the patient might have leukæmia was raised. No convincing evidence that this is so has been obtained.

Without transfusion the patient's hæmoglobin continued to fall, and in February, 1958, he was admitted to the Clinical Center of the National Institutes of Health. During his time in

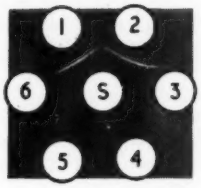

Fig. 1

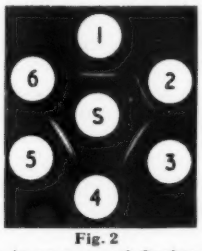

Fig. 2

Fig. 1—The precipitin reaction, seen in an agar-gel Ouchterlony plate, between the serum of the patient in the centre well and some, but not all, members of a panel of sera from normal persons. Unstained plate after 24 hours.

Fig. 2—The precipitin reaction between the serum of the patient in the centre well against some, but not all, members of a panel of sera.

The two degrees of positive reaction are shown: nos. 1, 3, and 5 are 2+ reactors and no. 2 is a weak + reactor.

hospital the patient had persistent anæmia without reticulocytosis. The leucocyte count varied from 10,000 to 15,000 and the platelet count was consistently above 500,000 per c. mm. The differential count showed predominantly neutrophils with a relative increase of immature forms. Bone X-rays showed no abnormalities. Refractory anæmia of unknown cause was diagnosed. The patient was given cells from 4 units of blood, which raised his hæmoglobin to 11 g. per 100 ml., and was discharged.

When the patient first received blood-transfusions in 1958 they were well tolerated. Since that time he has received 47 units of blood. The patient is of blood group AB, Rh+, and there has never been evidence of red-cell incompatibility with donor bloods. In the spring of 1960 the patient began to have transfusion reactions. Within about 1 hour of some, but not all, transfusions there was a fever, rising to 38–39°C (100·4–102·2°F) accompanied by headache and muscle pain, but no other symptoms. The fever and symptoms persisted for about

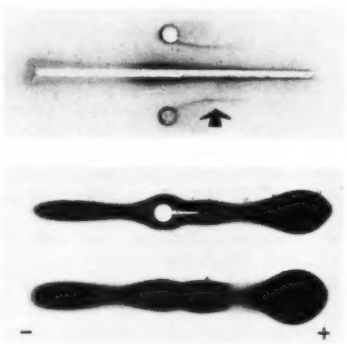

Fig. 3—Agar-gel immunoelectrophoresis to characterise antigen.

The serum of a strongly positive reactor was concentrated three times by ultrafiltration and submitted to electrophoresis. The serum of the patient was placed in the rectangular antibody well. The position of the precipitin line (arrow) suggests that the antigen is an α_2-globulin. Above, unstained precipitin lines; below, protein stain.

5 hours, and then slowly subsided. The patient had been discharged from hospital before the precipitin in his blood was discovered, so that it has not yet been possible to ascertain whether only bloods containing the precipitating antigen give transfusion reactions.

Precipitation Reactions

The serum of the patient gave well-defined precipitation reactions in agar with some, but not all, panel sera (fig. 1). The reaction was clearly visible at 18 hours and was intense after 2 days. The precipitation line was convex toward the centre (precipitin) well, indicating that the antigen is of relatively high molecular weight (Korngold et al. 1959). Two intensities of reaction were definable in most groups of sera studied (fig. 2). Some sera lacked detectable antigen, the precipitation lines extending into the corresponding wells without deviation (fig. 1). The precipitation lines were clear-cut and quite unlike the diffuse reaction which slowly develops between rheumatoid factor and γ-globulin in some subjects (Franklin 1960a). Rheumatoid-factor reaction was excluded because neither the patient nor most of the positive subjects had rheumatoid factor, as determined by bentonite-flocculation and latex-fixation tests. Some panel subjects with rheumatoid factor gave reactions with the antiserum, but others did not. A second sample of serum from the patient, drawn 3 weeks after the first, at a

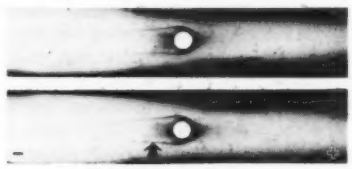

Fig. 4—Agar-gel immunoelectrophoresis to characterise the antibody.

The serum of the patient was placed in the circular wells and submitted to electrophoresis, and a strongly positive serum concentrated three times was placed in the rectangular wells. A broad precipitin line (arrow) is seen in the position of the γ-globulin.

time when the patient had not received any medication since discharge, gave identical reactions, as did a third sample drawn 1 month later, and a fourth 3 months later.

Support for the interpretation that the precipitin in the serum of this patient is an antibody came from experiments showing that the active protein is a 7S-γ-globulin. We propose the designation Ag(a+) for sera containing the α-globulin antigen and Ag(a−) for sera that do not contain the antigen. The precipitin in the serum of the patient thus has the specificity anti-Ag(a+).

Characterisation of Antigen

A panel serum giving a strongly positive precipitation line in the gel-diffusion test was concentrated three times by ultrafiltration and used for immunoelectrophoresis. The antibody well was filled with serum from the patient. A well-defined precipitation line developed between the α_2 region and the antibody (fig. 3). This result, along with that in the Ouchterlony plates, suggested that the antigen is a high-molecular-weight α_2-component. The only α_2-macroglobulin so far defined is the 19S-α_2 component described by Brown et al. (1954) and Wallenius et al. (1957), which appears to be equivalent to the slow-α_2 component found on starch-gel electrophoresis (Poulik and Smithies 1958). Purified α_2-macroglobulin (Behringwerke, Marburg) in a wide range of concentrations failed to give precipitation with the patient's serum.

Furthermore, when an Ag(a+) serum was submitted to starch-gel electrophoresis, the slow-α_2 fraction recovered by the technique of Gordon (1960) failed to show precipitation with the anti-Ag(a+) serum. The further identification of the antigen present in the α-globulin is currently being undertaken.

Characterisation of Antibody

The patient's serum was submitted to immunoelectrophoresis, and a serum giving a strong reaction in the Ouchterlony tests was placed in the side well. Within 18 hours a well-defined precipitation line appeared in the γ-globulin region (fig. 4). This result, together with the shape of the precipitation curve in the Ouchterlony plate, suggested that the antibody was a relatively low-molecular-weight γ-globulin. This interpretation was confirmed by an experiment in which the 7S- and 19S-γ-globulin components in the patient's serum were separated by density-gradient centrifugation. Precipitation lines in Ouchterlony plates were obtained with low-molecular-weight fractions giving no reaction with immune-rabbit serum against 19S human γ-globulin as described by Franklin (1960b). It can, therefore, be concluded that the antibody is a 7S-γ-globulin. The serum of the patient's daughter showed no reaction when tested against panel sera nor against her father's serum.

Stability of the Antigen

The antigen is unaffected by heating at 57°C for 40 minutes, by hæmolysis with its own or foreign human hæmoglobin, or by storage at room temperature for up to 7 days. The antigen was not lost by dialysis or ultrafiltration. Sera of either type (reacting or non-reacting) stored for as long as 4 years at −20°C were consistently found to give the same reaction as fresh sera from the same subjects. The reaction in the fresh sera, however, was in some cases stronger and better defined than in the stored sera. Repeated freezing and thawing of the sera up to at least fifteen times did not affect the reaction. Blood-samples were withdrawn twice weekly for 4 weeks from two normal volunteers whose sera reacted strongly with that of the patient. The reaction remained unchanged during this period. Sera withdrawn approximately twice yearly over a 2-year period from six subjects, two of whom reacted and four of whom did not, consistently gave the same reaction. Of 2 sera withdrawn in 1955, 1 was a reactor and the other not; the reactions in sera withdrawn from the same subjects in 1959 were unchanged.

Variation in the position of the slow-α_2-globulin after starch-gel electrophoresis has been noted. By means of vertical electrophoresis, using borate buffer at pH 8·6 (Smithies 1959), a slow-moving, a fast-moving, and a double band can be distinguished. It has been suggested that this variation may be due to storage (Smithies 1955); but this may not be the only explanation. Sera from different persons stored for the same length of time under identical conditions may show the variation, and not all stored sera show it (Blumberg 1961). In any event, this does not appear to affect the reaction with the patient's serum. Persons of each of the three slow-α_2-types were both positive and negative reactors.

It appears, therefore, that the antigen is relatively stable and persistent in any one person.

Distribution of the Antigen in Populations

Because the supply of antibody serum is limited, extensive population surveys have not been possible. However, positive and negative sera were found in all the populations studied. On the basis of preliminary examinations, the frequency seems to vary in different populations. The frequencies of positive reactors in some populations are shown in table I. More extensive studies are planned when micromethods are developed.

TABLE I—FREQUENCY OF POSITIVE REACTORS

Population	No. studied	No. positive
Parents of white U.S. families	56	32 (57%)
U.S. Negroes	21	10 (48%)
Micronesians (Rongelap, Marshall Islands)	51	50 (98%)

Inheritance of the Antigen

126 sera from 29 American families (25 white, 4 Negro) were studied. The results are shown in table II. In addition, 38 sera from 8 Micronesian families were tested. Since the frequency of positive reactors was high in the Micronesians, all of these were Ag(a+) × Ag(a+) matings, and nearly all the offspring were Ag(a+). These are also shown in table II, but are not included in the statistical evaluation, since they are not decisive in testing the genetic hypothesis. In the families from the United States, among the offspring of positive × positive and positive × negative matings, positive and negative offspring were found, whereas among the offspring of negative × negative matings only negative offspring appeared. This result suggests that the inheritance of the antigen follows mendelian segregation, with negative subjects homozygous for a recessive gene *Ag*, and positive subjects homozygous or heterozygous for the allelic gene Ag^A. It is suggested that the Ag^A gene controls the synthesis of the *Ag*(a+) antigen. If a product of the allelic gene is found, the gene could be termed Ag^B and the antigen *Ag*(b+).

TABLE II—INHERITANCE OF THE ANTIGEN

Mating type	No. of families	Offspring		Total
		Ag(a+)	Ag(a−)	
United States:				
Ag(a+) × Ag(a+)	11	21	5	26
Ag(a+) × Ag(a−)	10	9	13	22
Ag(a−) × Ag(a−)	8	0	20	20
Micronesian:				
Ag(a+) × Ag(a+)	8	21	1	22

The family data were analysed by the methods summarised by Smith (1956). In this, four types of comparison are made, in each of which a correction is included for family size. The comparisons of observed and expected figures involve:

1. The number of recessive Ag(−) children resulting from Ag(+) × Ag(−) matings, given the number of families in which there is at least one recessive child.
2. The number of recessives resulting from Ag(a+) × Ag(a+) matings in which there is at least one recessive offspring, given the total number of families with at least one recessive offspring.
3. In Ag(a+) × Ag(a−) matings, the total number of families with at least one recessive offspring, given the total number of Ag(a+) × Ag(a−) matings and the gene frequencies in the population from which the families were selected (q = frequency *Ag* = 0·66).
4. In Ag(a+) × Ag(a+) matings, the total number of families with at least one recessive offspring, given the total number of Ag(a+) × Ag(a+) matings and the gene frequency.

The first two computations are independent of the gene frequencies in the population study. For the third and fourth computations, however, an estimate is needed of the gene frequency in the population from which the families were drawn. We were unable to obtain a large random sample from the population from which the families were selected, and the gene frequency was estimated from the frequency of the phenotypes in the

TABLE III—OBSERVED AND EXPECTED NUMBERS OF Ag(a−) CHILDREN FROM VARIOUS MATINGS

Test	Mating	χ^2
Comparison of observed and expected number of Ag(a−) children in families where there is at least one Ag(a−) child	Ag(a+)×Ag(a−)	0·99
Comparison of observed and expected number of Ag(a−) children in families where there is at least one Ag(a−) child	Ag(a+)×Ag(a+)	1·37
Comparison of observed and expected number of families with at least one Ag(a−) child, assuming an Ag-gene frequency of 0·66	Ag(a+)×Ag(a−)	0·49
Comparison of observed and expected number of families with at least one Ag(a−) child, assuming an Ag-gene frequency of 0·66	Ag(a+)×Ag(a+)	0·03
Comparison of observed and expected number of recessives in Ag(a−)×Ag(a−) matings	Ag(a−)×Ag(a−)	0

$\Sigma\chi^2 = 2{\cdot}88$ with 5 degrees of freedom; $0{\cdot}8 > P > 0{\cdot}7$.

parental members of the families (table I). Of 56 parents, 57% were found to be Ag(a+).

The results of these computations are summarised in table III, which includes also the results of Ag(a−) × Ag(a−) matings. Although the numbers are small, this preliminary family analysis is consistent with the genetic hypothesis. On the basis of segregation in this group of families, no evidence of close linkage was found with the following blood-group systems and haptoglobins types: ABO, Rh, MN, Duffy, Kidd, and P. Analyses of 30 twin pairs to be reported elsewhere were also consistent with the genetic hypothesis.

Independence of the Ag and Other Known Inherited Systems of Serum-proteins

The reactions in the panel sera showed that the Ag reactions were independent of rheumatoid factor and of haptoglobin, transferrin, and γ-globulin types. The segregation of the *Ag*^{A} and *Ag* genes in families was also independent of these systems. Since the Ag(a +) factor is an α-globulin it is also independent of another recently described inherited γ-globulin system designated In$_v$ by Ropartz (1960). In collaboration with Dr. J. Hirschfeld, of Stockholm, Ag tests were carried out on 113 sera of known Gc types, which are distinguishable by immunoelectrophoresis (Hirschfeld and Beckman 1960). Positive and negative Ag reactions were found in subjects of Gc types 1–1, 2–1, and 2–2, the percentage of reaction being of the same order in all these groups. Hence the Ag system is independent of all other known inherited serum-protein differences. The Ag(a+) antibody is also distinct from the factor in normal human serum giving a precipitate in agar with red-cell hæmolysates (Peetom et al. 1960); the antigen in the latter case is not present in serum and does not react as an α-macroglobulin. The Ag factor is present in too many normal sera to be C-reactive protein; which in any case migrates in the γ-region in immunoelectrophoresis (Zach and Zimmermann 1959).

Discussion

The precipitin in the patient's serum defines the presence of a factor in some sera from all human populations so far tested. The antigen is an α_2-macroglobulin and the precipitin a 7S-γ-globulin. The presence of the antigen appears to be genetically determined, so that a new polymorphic system in human serum-proteins has been revealed.

Besides being of genetical and anthropological interest, the finding of a specific precipitin in the patient's serum suggests that isoimmunisation by human serum-proteins may occur. Though there is no direct evidence that the precipitin was induced by the many transfusions which the patient received, this would seem to be the most probable explanation of the findings. In all, 61 sera of subjects who had received multiple transfusions have been tested, and 3 of these have given definite precipitation lines with some of the panel sera. The reaction which is the subject of this paper was the strongest, and the specificity of the others, which are different from the Ag system, will be reported later. Sera of forty persons who had not received transfusions failed to give precipitation lines with the panel sera.

Though our patient initially tolerated transfusions well, during the past 2 years he has had pyrexical reactions after most, but not all, transfusions. Whether these reactions take place only when donor serum is Ag(a+), and represent an antigen/antibody reaction, is now being investigated. Other properties of the precipitin will be described elsewhere. The unusual history of this case may be irrelevant, since the other subjects showing precipitins had typical thalassæmia.

Summary

A serum from an anæmic patient who had received approximately 50 transfusions was found to give strong precipitation with sera of some, but not all, normal subjects.

It appears that an antigen/antibody reaction is involved. The antigen in some normal subjects is an α_2-globulin, and the antibody in the patient is a 7S-γ-globulin. The antigen appears to be inherited according to simple mendelian rules and its frequency varies in different racial groups.

It is possible, though not proven, that antigen/antibody reactions were responsible for severe post-transfusion reactions in the patient, and similar processes may be involved in other unexplained post-transfusion reactions.

We are indebted to Dr. Fred Stohlman and Dr. Archie McKinney for supplying the serum from the patient; to Dr. Sheldon Dray and Dr. Kurt J. Bloch for valuable help and advice; to Dr. J. Hirschfeld, Stockholm, for collaboration with the Gc tests; to Dr. George A. Silver, Montefiore Hospital, New York, for allowing access to families under his care; to Dr. Arthur G. Steinberg for supplying blood from American Negro families and carrying out the γ-globulin typing; and to Dr. Lyman Crittenden for assistance with the linkage studies. Most of this investigation was undertaken while one of us (A.C.A.) was a visiting scientist at the National Institute of Arthritis and Metabolic Diseases.

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OBSERVATIONS ON THE SATELLITED HUMAN CHROMOSOMES

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EARLY analyses of the normal human chromosome complement by several independent groups suggested that two pairs of autosomes are characteristic in that they possess satellites on their short arms (Tjio and Puck 1958, Chu and Giles 1959, Levan and Hsu 1959). The larger pair was considered to be either the 13th or 14th largest autosomal pair; and the smaller, the 2nd smallest autosomal pair. The number of satellited chromosomes was increased to three pairs by 1960, when the authors of the Denver report on chromosome nomenclature (*Lancet* 1960) included both the 13th and 14th largest autosomes.

On the basis that only one of the two smallest pairs of autosomes was satellited, the autosome trisomic in mongolism was established as no. 21 Böök et al. 1959, (Lejeune et al. 1959).

During recent months we have been impressed by the much higher frequency of satellited chromosomes in our material, and by the behaviour and variable morphology of the satellites. We present here evidence that five pairs of chromosomes in man are satellited. We also report for the first time observations concerning a phenomenon, peculiar to satellited chromosomes, which we have termed *satellite association*. We believe that this phenomenon is important in the causation of many of the recently reported human chromosome abnormalities.

Methods

Our observations were made on preparations from short-term culture of white blood-cells from the peripheral blood (Osgood and Brooke 1955), using 'Bactophytohemagglutinin' (Difco) to facilitate separation of the leucocytes and plasma from the erythrocytes, and 'Colcemide' (Ciba) to accumulate mitoses in the culture.

Five female patients were used in the study. Three of them (cases 1, 2, and 3) are without recognisable chromosome anomalies; while two were cases of gonadal aplasia (case 4 chromatin-positive, case 5 chromatin-negative). Preparations from male patients were excluded to avoid possible confusion in the counts between the smallest group-VII autosomes and the Y chromosome. We have found no evidence of a sex-difference in the number or behaviour of the satellited chromosomes.

In each patient 50 cells were examined for satellited chromosomes and for instances of satellite association. The cells were selected only in so far as they were judged to be unbroken and to show no gross overlapping of chromosomes. Cells were excluded after counting only if they were found to be short of chromosomes in groups IV or VII. A satellited chromosome was defined either as one which showed a secondary constriction with distinct chromatin knobs projected from the arms on slender stalks, or as one which showed clear evidence of negative heteropyknosis at the ends of the chromosome arms.

Results

No satellites were seen on chromosomes of groups other than IV (chromosomes nos. 13, 14, and 15) or VII (chromosomes nos. 21 and 22). Each of the 250 cells examined contained at least one chromosome with visible satellites. In 28 cells all group-IV chromosomes, and in 62 cells all group-VII chromosomes, carried satellites (table I and fig. 1). 41% of cells had at least 5 satellited chromosomes in group IV, and 66% of cells had at least 3 satellited chromosomes in group VII, indicating that all chromosome pairs in both groups were potentially satellited in these cells. In the total counts (table II), 68% of all the group-IV chromosomes, and 70·5% of all the group-VII chromosomes had visible satellites.

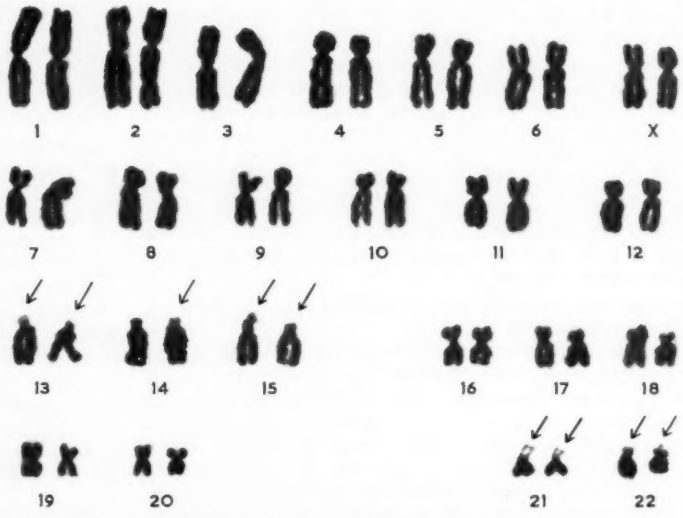

Fig. 1—Karyotype in case 1: 2n=46 (XX.) Satellites are visible in chromosomes 13, 14, 15, 21, and 22 (Aceto-orcein, reduced to ×2000 from ×4000).

TABLE I—NUMBER OF CELLS WITH SATELLITED CHROMOSOMES

Case	Number of chromosomes observed to have satellites in each cell													
	Group-IV chromosomes								Group-VII chromosomes					
	0	1	2	3	4	5	6	Total number cells	0	1	2	3	4	Total number cells
1	0	1	8	10	18	12	1	50	0	0	10	22	18	50
2	0	0	2	17	22	8	1	50	2	5	19	18	6	50
3	0	0	1	4	7	26	12	50	0	2	10	22	16	50
4	0	1	7	9	16	12	5	50	1	5	20	18	6	50
5	0	0	2	7	15	17	9	50	0	1	11	22	16	50
Total number of cells with satellited chromosomes		2	20	27	78	75	28	250/250		13	70	102	62	247/250

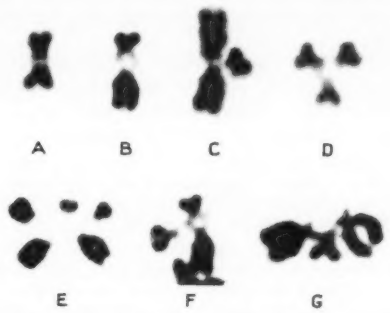

Fig. 2—Various types of satellite association selected from different cells:

A, double association between two group-VII chromosomes; B, double association between group-IV and group-VII chromosomes; C, double association between two group-IV chromosomes, with a group-VII chromosome adjacent; D, triple group-VII association; E, quadruple association of two group-IV and two group-VII chromosomes with unsatellited chromosome no. 18 nearby; F, double association between group IV and VII with one group-VII adjacent; and G, triple association of one group-VII and two group-IV chromosomes (Aceto-orcein ×4000).

Chromosomes which appeared to be attached to one another by their satellites were considered to show definite satellite association. 60% of cells showed at least one instance of this phenomenon. The type of association most often seen was double association (tables III A and B) where the chromosomes were linked by their short arms like a pair of acrobats (fig. 2 A, B, C, F). Triple association (fig. 2 D, G) and quadruple association (fig. 2 E) were also seen, the chromosomes being linked by their satellites as though holding hands in a circle. In other cells satellited chromosomes were unattached, but lay close to one another as if separated in the technical process of spreading (fig. 2 C, F). The frequency of this type of association is shown in the column " adjacencies " in table III B. Association was seen as often between chromosomes of the two groups as within each group.

Discussion

While we have found the peripheral blood-culture technique particularly favourable for study of the satellites, we have made similar observations, though with greater difficulty, in material derived from other sources including bone-marrow. The quality of preparation is reflected in the counts, particularly of satellite associations, and this is shown (table III B) by the greater number of " adjacencies " in cases 1 and 2 as compared with cases 4 and 5, in which the preparations were technically superior. We conclude that at least five pairs of autosomes are satellited in man. We have found no evidence of an individual variation in the number of satellited chromosomes.

The presence or absence of satellites can no longer be used as a criterion for identifying a chromosome pair; thus, the specific identity of the group-VII chromosome trisomic in mongolism is still in question.

The association of satellited chromosomes is so often seen that it suggests that the satellites possess a special property of adhesion, a property which is probably directly related to the formation of nucleolar material in the region of the satellite. Satellite association and nucleolar fusion are probably manifestations of the same phenomenon. We propose the hypothesis that satellite association is one of the determining factors in the production of autosomal non-disjunction during meiosis and possibly during the early divisions of the zygote. (Aneuploidy involving the sex chromosomes would seem to be better explained by precocious disjunction than by

TABLE II—NUMBER OF SATELLITED CHROMOSOMES IN 250 CELLS

Case	Group-IV chromosomes			Group-VII chromosomes		
	Number chromosomes satellited	% Satellited	Mean number satellited per cell	Number chromosomes satellited	% satellited	Mean number satellited per cell
1	185	62	3·7	158	79	3·2
2	189	63	3·8	121	60	2·4
3	244	81	4·9	152	76	3·0
4	196	65	3·9	123	61	2·5
5	217	72	4·3	151	76	3·0
Totals	1031/1500	68	4·1	705/1000	70·5	2·8

TABLES IIIA AND B—SATELLITE ASSOCIATION IN 250 CELLS

A—Number of associations

Case	Double association				Triple association	Quadruple association	Sextuple association
	IV–IV	IV–VII	VII–VII	Total			
1	4	11	6	21	3	1	1
2	3	7	2	12	5	0	0
3	11	24	4	39	5	3	0
4	7	27	4	38	11	1	0
5	22	29	18	69	9	0	0
Total	47	98	34	179	33	5	1

B—Total scores*

Case	Double association	Triple association	Quadruple association	Sextuple association	Total score		Total " association "
					Association	Adjacencies	
1	21	6	3	5	35	65	100
2	12	10	0	0	22	62	84
3	39	10	9	0	58	43	101
4	38	22	3	0	63	27	90
5	69	18	0	0	87	12	99
Total	179	66	15	5	265	209	474

*Triple association is scored as 2, quadruple association as 3, and sextuple association as 5, instances of satellite association.

non-disjunction.) On the same lines, we suggest that the probability of reciprocal translocation is greater between satellited chromosomes than between unsatellited chromosomes if chromosome breakage occurs in conjunction with satellite association. Possibly, chromosomes involved in satellite association may be more liable to breakage.

The five published examples of translocation in man (Turpin et al. 1959, Polani et al. 1960, Fraccaro et al. 1960, Penrose et al. 1960, Lejeune et al. 1960) may be taken as evidence for our hypothesis, because in each instance the structural anomaly may be interpreted as involving chromosomes in group IV and VII. In addition, two of the three confirmed examples of autosomal trisomy in man involve satellited chromosomes (Lejeune et al. 1959, Patau et al. 1960, Smith et al. 1960).

Many cytological observations by different workers suggest strongly that the nucleolus arises near the satellite by the activity of a nucleolar organiser. Satellited chromosomes have thus been considered " nucleolar chromosomes ". If this is true, as seems likely, satellite association may serve as an explanation of the puzzling observations on the " nucleolar chromosome " made on human pachytene chromosomes by Schultz and St. Lawrence (1949), and later confirmed by Yerganian (1957). These workers identified a particular bivalent by the presence of a prominent nucleolus associated with a specfic chromosome region. A comparison of a number of these nucleolar chromosomes revealed that while in many cases the nucleolus appeared in a medial position, in almost an equal number of figures the nucleolus was either terminal or subterminal. The suggestion was made that the nucleolar chromosome was broken in those figures in which it was not in a medial position. From a study of the illustrations accompanying these reports, and in view of the evidence which we present, the most likely interpretation is that the pachytene chromosome with the medial nucleolus was in fact two satellited chromosomes whose terminal nucleoli were fused. When the nucleolus is seen to be terminal, only one satellited chromosome is implicated. It seems no longer necessary to relate the number of satellited chromosomes directly to the number of nucleoli visible in the intermitotic nucleus.

Further confirmation of the phenomenon of satellite association is given by the published photographs of other workers (e.g., Ford 1960), and by other independent observations (Patau 1960).

One of us (S. D. H.) is at present investigating the chromosomes in the Marfan syndrome, in view of the interesting observations of Tjio et al (1960) that familial cases of the syndrome are associated with satellite enlargement. Arising out of this investigation is a strong impression that the size of satellites on any particular chromosome is a characteristic of the individual's karyotype and is itself not necessarily associated with congenital disease. In cases showing such distinctive satellite morphology, family studies will be made and blood-group and other marker traits determined for purposes of linkage analysis.

Summary

Counts of satellited chromosomes in 250 cells from peripheral blood-cultures in five persons reveal that chromosome nos. 13, 14, 15, 21, and 22—the five pairs of chromosomes in group IV and VII—are satellited. Assuming that this is the normal situation in man, the specific identity of the autosome trisomic in mongolism is questioned.

Evidence is presented in support of *satellite association*, a hitherto undescribed phenomenon, which was observed in 60% of mitoses. This finding is discussed in relation to the cause of human chromosome anomalies.

We are grateful to Yvonne Phillips Hajda and Bonny Morgan Lewis for their technical assistance, and to our colleagues for their advice and criticism; in particular we thank Dr. Victor A. McKusick, Dr. William J. Young, and Dr. Alan W. Johnston.

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TREATMENT OF INORGANIC MERCURY POISONING WITH N-ACETYL-D, L-PENICILLAMINE

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DESPITE advances in pharmacology, the treatment of chronic mercury poisoning remains largely empirical and reports on the reliability of the various remedies suggested are conflicting (Hunter 1955, Spiegl 1956, Hamilton 1945, Johnstone 1948, Henderson and Haggard 1943, Bell et al. 1955). Furthermore, some of the agents carry a distinct hazard of their own and may do more harm than good.

Such therapeutic confusion suggests that a reliable drug has yet to be brought into established clinical usage. Laboratory experiments show that N-acetyl-D, L-penicillamine is more effective than other penicillamine derivatives in protecting the laboratory animal from induced inorganic mercury poisoning and that its toxicity is also considerably less (Aposhian 1959). Because of this the following case is presented in an attempt to persuade other workers to evaluate similar treatment in man.

Though the disease is exceptionally rare in this country today and control of mercury vapour in industry is well established, it may be a hazard in physiological and medical laboratories if certain well-defined precautions are not adhered to (Noe 1959).

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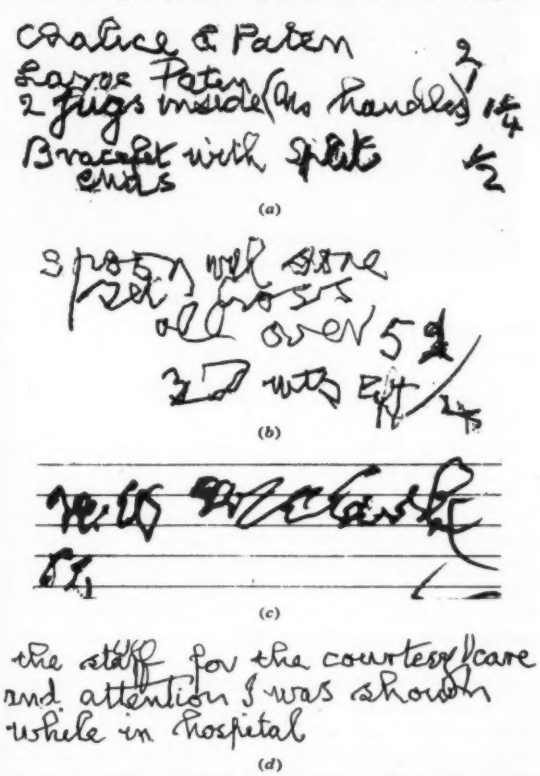
Case-report

The patient, a man of 56, had worked for fifteen years as a gilder in a small factory in the heart of London. He was the only employee engaged in this craft, and when he was seen as an outpatient he could well have been the only active hand-gilder in Great Britain.

The process entailed lighting a charcoal fire in the mouth of a small brick chimney in an area enclosed with glass and about 2 ft. square. The exhaust mechanism was grossly inadequate. When the fire was well alight, a crucible containing a small quantity of gold and a rather greater quantity of mercury was put on it. When hot enough the gold melted into the mercury making a tough putty-like paste, gold-mercury amalgam. The amalgam was then emptied into a dish containing water. Two further dishes contained respectively a weak nitric acid solution with a quantity of mercury at the bottom, and mercury with a tiny amount of gold, lying under water. The article to be gilded was held over the bowl with the weak acid solution and the small quantity of the mercury lying beneath the acid scooped up in a clay-pipe and poured over it. This process was called " quicking-it ". The acid was removed by rinsing the article under tap-water. From the second bowl a quantity of the mercury with a little gold in it was then scooped out and poured over. This was called " putting it through the slack ". The article was then ready to take the amalgam; the latter was placed into a piece of stocking which was squeezed tightly around the lump, and dabbed all over the work piece. This deposited a light covering and was known as " charging ". The amalgam was next spread evenly with a brush—" bringing it off ". The article, held in tongs, was heated in the charcoal fire. From time to time it was taken off and gently brushed. The mercury was driven off as a vapour. At the critical time—" as she began to blow "—the surface acquired a shiny white sheen. This gave place to a pale-yellow colour denoting the right time to remove the article from the fire. During gilding the article was brushed from time to time, and examined carefully under a bright light. The real art of gilding lies in knowing the right time to use the brush and how much to use it.



(*a*)

(*b*)

(*c*)

(*d*)

Specimens of patient's handwriting: (*a*) 3 months before onset of symptoms; (*b*) at the time of onset; (*c*) signature on arrival at outpatients 3 months after (*b*); and (*d*) 4 weeks after completion of treatment.

History.—When he was referred to hospital the patient had been attending his doctor for a month with tremor. This tremor had first appeared three months previously and had progressively worsened. It was now so bad that his wife had obtained a set of plastic crockery as he had broken most of her collection of china. He had had great difficulty in performing small tasks with his hands, though he had not been forced to give up his work. His diary showed gross deterioration in his handwriting over the preceding few months (see figure). The patient denied any change in his mentality, though he admitted that he might have been a shade more irritable during recent weeks. He generally conducted the gilding process about twice a week and had noticed a nasty metallic taste in his mouth after exposure to the fumes. During the preceding two years his gilding activities continued to be carried out twice a week, but the amount of work he did at each session was greater. The formation of new independent African States had led to his firm being employed to hand-gild various articles of State authority—e.g., a large gold mace. There is no doubt that this recent influx of work was a major contributing factor in the production of his " shakes ". The social history showed that he drank virtually no alcohol and drank at least a pint of milk daily. He smoked 20 cigarettes per day. Twelve years previously all his teeth had become loose and had been extracted. The man who had previously been doing the same job as the patient had died of mercury poisoning and an inquest had been held. The cause of death was certified as nephrosis leading to uræmia.

Clinical examination.—The patient was a good witness without any evidence of emotional lability. There was gross intention tremor of both hands and milder tremor of the head and eyebrows. There was slight ataxia of the gait. His handwriting was completely illegible (see figure). There was some degree of dysphonia. The remainder of the physical examination was entirely normal and failed to reveal any of the other stigmata of mercury poisoning. Slit-lamp examination (Mrs. Dorothy Miller), however, showed blue-grey mottling of the corneal endothelium with a polychromatic lustre of the post-lens capsule. Furthermore, examination of the larynx (Mr. Maxwell Ellis) showed that the cords moved rather jerkily, and it was felt that the hoarseness was due to incoordination. There was no albuminuria.

Investigations on admission showed hæmoglobin 99%, white blood-cells 6000 per c.mm., erythrocyte-sedimentation rate 4 mm. in first hour (Westergren) with a normal blood-film. X-rays of the chest and skull were normal. Chromatography of the urine did not show any abnormal quantity or distribution of aminoacids. An electrocardiogram was normal. An electroencephalogram (E.E.G.) showed a mild paroxysmal instability only.

Treatment with N-acetyl-D, L-penicillamine in a dosage of 250 mg. four times daily was started and was continued for ten days. The urine was carefully examined for albumin throughout this course but none was detected at any time. After a rest period of seventeen days, the patient was given a further ten-day course of the penicillamine compound and was discharged. At this point it was felt that great clinical improvement had taken place, and the patient himself commented on the noticeable alleviation of many of his symptoms.

Urinary mercury estimation, before the onset of treatment, showed that he was excreting 1369 μg. of this metal daily. During the first course of therapy two further twenty-four-hour samples (second and sixth day) were obtained and estimation showed that the mercury excretion had risen to 1828 μg. and 1639 μg. respectively. The second course of therapy produced a dramatic fall in mercury output, 600 μg. and 420 μg. being excreted on the second and sixth days.

Nineteen days later a third course of treatment was begun, again 250 mg. four times daily for ten days. After this a further

twenty-four hour specimen of urine was sent for mercury estimation and the excretion was found to be 290 μg. daily. The patient's clinical condition had continued to improve throughout this time and the tremor was much less. One month after discharge he had almost recovered with very little clinical evidence of mercurialism. The E.E.G. retained a mild paroxysmal instability. Examination of the larynx was normal.

Discussion

There is no doubt that this patient had classical chronic mercury poisoning. Apart from the relation of symptoms to occupation, the urinary mercury level was grossly raised. The normal is almost certainly below 100 μg. daily (Hunter 1955). The patient had dysphonia as part of the clinical picture. This is not usually recognised as part of the mercurialism complex, but has been described (Faleg and Lenzi 1959). Furthermore, he had a gross tremor in association with a very small intake of alcohol. This, again, is at variance with some observers (Hunter 1955).

The decision to use a penicillamine compound was taken because of the uncertainty in the published reports of the efficacy of other chelating agents. The experimental reliability of N-acetyl-D, L-penicillamine encouraged us to use this particular drug in preference to other similar ones. The exact mode of action of this compound still remains in doubt, but presumably it acts by binding mercury to the —SH group (Walshe 1960). Though this patient's urinary level of mercury rose considerably during the first course of treatment, the amount of the metal excreted may well be very much less important than the amount complexed in an inactive form in the blood and tissues. The rapid fall in mercury output during the second and third courses of treatment seems to support this explanation. On clinical grounds it was felt that the patient's improvement was due to therapy and not just to removal from his environment. It is, of course, impossible to be dogmatic about this, but in those cases of untreated chronic mercurialism which recover a period of months rather than weeks is required (Hunter 1955).

Summary

A case of chronic inorganic mercury poisoning in a hand-gilder was successfully treated with three ten-day courses of N-acetyl-D, L-penicillamine, 250 mg. four times daily.

Though this disease is nowadays rare, it remains a potential hazard in medical and scientific laboratories.

It is suggested that N-acetyl-D, L-penicillamine represents a real advance in the management of this condition, and it is hoped that any future cases of mercurialism will be treated similarly for clinical comparison.

We are grateful to Dr. R. J. Porter, under whose care the patient was admitted, for much helpful criticism. Dr. T. O. Garland dealt with the industrial aspects and proved a constant stimulus. The urinary mercury levels were estimated both by the department of industrial disease of The London Hospital and by the laboratories of the Ministry of Labour; their assistance proved invaluable. The N-acetyl-D, L-penicillamine was supplied by the Distillers Company Ltd.

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AN OXYGEN-DRIVEN BLOOD-INFUSION PUMP

Performance and Use in Exchange-transfusion

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MOST of the pumps used to infuse blood rapidly into arteries or veins achieve the necessary pressure by mechanically squeezing the blood during its passage along a relatively narrow tube and this damages the red blood-cells. In the apparatus described here a gentler principle is used: the driving-force is compressed oxygen.

The pump (fig. 1), complete with cylinder, weighs 14 lb., measures 14 × 14 × 8 in., and is assembled on a tray. The pump is driven by an 18-gallon oxygen cylinder fitted with a pressure-regulator, and a safety valve which

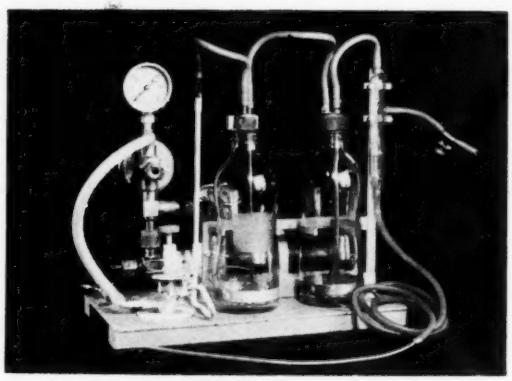

Fig. 1—The assembled pump.

limits the maximum pressure to 30 lb. per sq. in. The regulator carries a cylinder-contents gauge and a reduced-pressure gauge (fig. 2). The static pressure of the regulator is adjustable, but is usually set at 10 lb. per sq. in. The outlet of the regulator is connected by pressure tubing to tap A (fig. 2). Tap A has two controls, B1 and B2. When the cylinder is turned on and tap B2 is in the "on" position, a fine control of flow is possible using valve B1. If the flow of blood has to be stopped quickly, control B2 is moved to the "off" position. This will cut off the supply of oxygen and also allow the pressure from the bottles to be released (insert, fig. 2). The sterile parts of the apparatus are attached to the oxygen supply by a spring-loaded connector E, which also serves as an additional safety-valve. The standard blood bottles are connected by two sets of stainless-steel tubes—one long, one short—fixed into the metal screw-caps, the seal being made by the usual rubber washers. An Oxford safety-dripper (Macintosh and Pask 1941) is fixed to the outlet of the bottle. The safety dripper has a tube G with a clamp, which allows the drip-chamber and the tubing leading to the patient to be primed. Should both bottles become

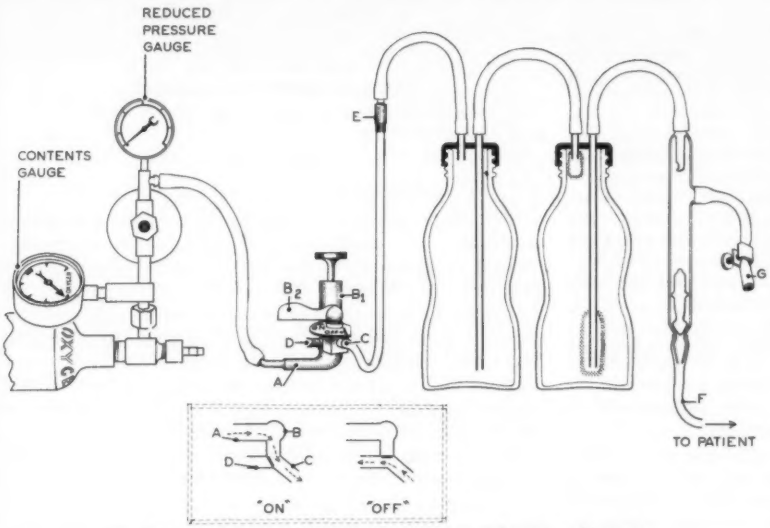

Fig. 2—Circuit-diagram of pump (see text for explanation of letters).

empty, the safety-dripper float will fall and seal off the tube to the patient. This prevents oxygen from passing, while leaving the tube to the patient filled with blood.

When the infusion begins, both bottles are filled with blood. The infusion is stopped before the bottle nearest to the oxygen supply is completely emptied. This bottle is then changed and the infusion is continued. Frothing does not take place.

Performance of the Pump

Rate of Infusion

Fig. 3 shows that the outflow of blood from the pump, over its useful range, rises more or less linearly with the applied pressure and that under experimental conditions, resembling

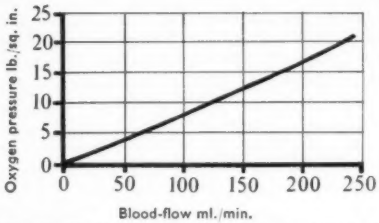

Fig. 3—Relation of oxygen pressure to blood-flow from oxygen pump with needle (S.W.G. 17) attached.

those of an infusion, a pressure of 10 lb. per sq. in. gives a flow-rate of approximately 120 ml. of blood per minute.

Amount of Hæmolysis

The increase in the plasma-oxyhæmoglobin level of blood flowing out of the pump under differing experimental conditions was determined by comparing, in a 'Unicam' spectrophotometer SP 500, the extinction-coefficients at 540 μ and 578 μ with those of plasma from the same pooled blood before its passage through the pump. The calibration curves were set up at each wavelength using dilutions (in 0·048% w/v ammonia solution) of blood of known hæmoglobin level; from these, the two values were calculated and the mean was taken. All plasma samples were obtained by double centrifugation of blood. No hæmoglobin derivatives other than oxyhæmoglobin were demonstrable spectrophotometrically in plasma after the passage of blood through the pump.

Table I shows the increase in plasma-oxyhæmoglobin level when blood was passed through the oxygen pump, and compares it with that found with a rotary pump under given conditions. Without the infusion needle, both pumps caused little hæmolysis, but with the infusion needle in place the hæmolysis at flow-rates near 250 ml. per min. increased by only about 40% when the oxygen pump was used, whereas an increase of about 400% took place with the rotary pump.

Dissolved Oxygen Content of Infused Blood

In the bottle next to the oxygen supply (fig. 2) only the surface layer of blood is exposed to oxygen at high pressure, and since this layer never passes over into the second bottle the problem of its dissolved oxygen content should never arise. At 10 lb. per sq. in. the increased amount of oxygen in physical solution would be of the order of 3·5 ml. per 100 ml. of blood, and at 20 lb. per sq. in. it would be 5·0 ml. per 100 ml., so that even if, by mismanagement, blood exposed to this oxygen pressure were infused intra-arterially or intravenously, no harm would result. The use of compressed air, instead of oxygen, to drive the pump should, however, be avoided, as the increased amount of dissolved nitrogen might lead to evolution of gaseous nitrogen in the blood-stream should blood in contact with compressed air accidentally be infused. For this reason the volumes of air left in the drip-chamber and in the bottle next to it should either be kept to about 20 ml., or else be displaced by oxygen before infusion begins.

TABLE I—COMPARISON OF THE AMOUNT OF HÆMOLYSIS PRODUCED IN BLOOD DURING PASSAGE THROUGH A ROTARY PUMP AND THROUGH THE OXYGEN PUMP

Rotary pump		Oxygen pump		
Blood-flow (ml. per min.)	Plasma hæmoglobin (mg. per 100 ml.)	$_sO$ pressure (lb. per sq. in.)	Blood-flow (ml. per min.)	Plasma-hæmoglobin (mg. per 100 ml.)
Without giving needle:				
228	24·8	..	..	..
265	26·4	7	255	25·8
319	31·4	8	393	27·2
..	..	10	558	34·6
With giving needle (S.W.G. 17):				
250	104·6	10	118	20·8
260	127·2	14	180	26·0
277	145·6	21	234	35·2

TABLE II—HÆMATOLOGICAL INVESTIGATIONS DURING EXCHANGE-TRANSFUSION

Sample	Bottles of blood exchanged	Hb (%)	Hæmatocrit value (%)	Platelets (per c.mm.)	White blood-cells (per c.mm.)	Clotting-time (min.)	Prothrombin-consumption index	Inhibitor units per ml.
1	0	53	25	430,000	6700	70–120	..	35–50
2	3	55	27	425,000	6500	42–44	125	..
3	6	80	38	368,000	6650	24–28	139	..
4	9	85	38	258,000	6850	21–33	141	5·7
5	12	85	39	328,000	6050	24–29	143	5·9
6	15	92	39	285,000	5360	23–30	149	..

Sterility

We suggest that compressed oxygen should be blown through the non-sterile parts of the apparatus before infusion begins. Thereafter the risk of contamination is no greater than in an ordinary blood-transfusion.

Safety

No part of the apparatus will break at the pressures of up to 30 lb. per sq. in. that are permitted by the reducing valve. The pressure tubing will withstand about 60 lb. per sq. in. Tests of the glass bottles with a Murray hydraulic dead-weight tester Mark IA showed that the new straight-sided bottle (Code no. G152 HH) broke down at an average pressure of 200 lb. per sq. in. and the old waisted bottle (Code no. G146 AB) broke down at an average pressure of 300 lb. per sq. in.

Use of the Pump

The pump is intended for use in intra-arterial infusion and for exchange-transfusion in the adult, but has not yet been used for the former purpose. The following is an example of its use in exchange-transfusion.

A hæmophiliac, whose plasma also contained an abnormal anticoagulant, appeared in danger of asphyxiation from a mediastinal hæmatoma. It was decided to try to reduce the level of the circulating anticoagulant by exchange-transfusion.

To achieve a concentration of 86·5% of the transfused blood within the patient, 10 litres of blood must be exchanged (Bessis 1949). This may be done by injecting the blood into one arm and bleeding from the other, or by using the same vessel for injection and for bleeding. Since a suitable infusion-pump was available and as many of the patient's veins as possible had to be conserved, the second method was chosen. A no. 4 polyethylene cannula was passed into the right axillary vein and connected to a Y-tube, one arm of which was connected to the infusion-pump and the other to a gentle suction apparatus. In this way, by alternately clamping and releasing the arms of the Y-tube, it was possible to infuse and to extract blood. 1 pint of blood was taken off before 1 was infused and this was continued until a 10-litre exchange had been completed.

Initially, extraction took approximately 3–5 min. per pint and infusion a similar time. 4 litres were exchanged in 67 min. The extraction of the 9th pint proved, for some undetermined reason to be very difficult, and 2 pints were, in fact, infused while the 9th pint was being extracted intermittently over a period of 80 minutes. There was no further difficulty in the extraction of blood, though the time taken slowed to 10–15 min. per pint, and the infusion-time to about 7 min. per pint. Hence, the remaining 5·5 litres were exchanged in 208 mins.

Calcium gluconate, 1·5 g., was given before the infusion of every pint, but after the eighth dose the patient vomited. Since further doses produced more vomiting later in the exchange, the dose was halved. During the whole procedure the serum-calcium remained normal.

Blood was taken for hæmatological and clotting investigations after every third bottle of the exchange and the results are shown in Table II.

Next day the patient was much improved. There was no hæmoglobinuria and no detectable increase of plasma-hæmoglobin or plasma-bilirubin after the exchange-transfusion.

Summary

An oxygen pump is described which has been used clinically to infuse blood at rates of up to about 250 ml. per min. without causing detectable hæmolysis. Its performance in laboratory tests indicates that it possesses an advantage over rotary pumps. A simple safety device protects against gas embolism.

We thank Dr. P. C. Mallam for permission to publish clinical details of the patient and Dr. R. G. Macfarlane for permission to quote the hæmatological findings.

Any inquiries regarding this apparatus should be made to H. G. East & Co., 37A, Oxford Road, Cowley, Oxford.

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NEONATAL VARICELLA

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VARICELLA, though common in older children, is rare in neonates. It is usually assumed that passive immunity, which is transferred to the fœtus, lasts for some months (Harries and Mitman 1951). The evidence for this immunity is, however, not as conclusive as with measles. If the mother has previously had an attack of varicella, one would expect the child to be immune for the first few months of life. If she had not had an attack, one would expect her either to contract the condition at the same time as the baby, or to contract it from the baby.

Intrauterine infection has been reported on several occasions—both mother and baby being affected.

Varicella developing on the 8th day of life was reported by Henderson (1934). Shumann (1939) reported varicella in an infant 2 days old. Oppenheim (1944) reported the case of a woman 7 months pregnant who had varicella; premature labour followed 5 days later, and the baby showed the lesions on the 7th day of life and died on the 16th day with widespread visceral lesions. Ehrlich et al. (1958) found a total of 16 published cases in the first 10 days of life. These represent intrauterine infections and carry a poor prognosis, the fatality-rate approaching 20%.

We could find no published cases of extrauterine infection in the neonatal period, and so we report 2 cases, in both of which the presence of varicella virus was confirmed.

Case 1.—The mother had had varicella when she was 4 years old. The confinement was at home, and pregnancy and labour were normal. The mother had no illness or skin lesion during pregnancy or puerperium. On the day before confinement the patient's brother showed the lesions of varicella. On the 14th day of life the baby had vesicopapules scattered all over the body and also in the mouth (see figure). He had mild pyrexia for 48 hours. The lesions ran a normal course and the child was never very ill. He was discharged at the age of 8 weeks, perfectly fit.

Varicella in 14-day-old infant (case 1).

Case 2.—The mother could not find out whether she had ever had varicella. Normal full-term pregnancy ended with home confinement. The mother had no illness or skin lesion during pregnancy or puerperium. The patient's sister had varicella on the 1st day of the baby's life. The infant showed the lesions on the 12th day of life; but he was never ill, and was not admitted to hospital.

Discussion

These cases suggest that the prognosis for neonatal varicella, contracted after birth, is good, possibly because of partial immunity derived from the mother.

The antibody-neutralisation titres of the mothers' serum were kindly estimated in the department of bacteriology of Liverpool University. These were normal for immune adults. This suggests that the normal transference of passive immunity to the fœtus did not take place in these

2 infants. The rarity of cases at this age suggests that this mechanism scarcely ever fails.

Summary

In 2 cases of neonatal chickenpox, contracted after birth, the mothers had normal immune serum, but had failed to pass on adequate passive immunity to the fœtus.

We should like to thank Prof. A. W. Downie, F.R.S., Dr. Kevin McCarthy, and Dr. A. Caunt, of the department of bacteriology of Liverpool University, for their help with these patients.

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HERNIATION OF THE HEART AFTER INTRAPERICARDIAL PNEUMONECTOMY

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INTRAPERICARDIAL dissection after removal of a segment of pericardium is often performed during pneumonectomy for bronchial carcinoma. Grave complications include various cardiac arrhythmias and herniation of the heart through the pericardium (Bettman and Tannenbaum 1948, Kirchoff 1951, Higginson 1953, Dahlbäck and Nilsson 1956, Sharma et al. 1959). An unusual case of cardiac herniation, causing ventricular fibrillation, successfully treated by cardiac massage and mouth-to-mouth artificial respiration, is reported here.

Case-record

In the course of a left intrapericardial pneumonectomy on a man aged 40 on account of carcinoma of the left lower lobe, an oval piece of pericardium, about 7·5 × 5 cm., had been excised. The patient left the operating-theatre at 6·45 P.M. I was called urgently to the ward at 7 P.M. and found the patient cyanosed and pulseless, with widely dilated pupils. He was gasping only occasionally. Within a minute, while preparations for immediate thoracotomy were being made, his breathing became more rapid and regular, and the pulse became palpable. It was then noticed that the drainage-tube had been connected to a continuous-suction apparatus. This was disconnected. The apex beat was unduly prominent and higher than usual, the systolic blood-pressure was 75 mm. Hg, and the peripheral circulation was poor; but his condition seemed to be improving, and we assumed that his hypotensive episode had been caused by a mediastinal shift due to suction. We anticipated spontaneous improvement, and the chest was not opened.

During the next hour the systolic blood-pressure did not rise above 80 mm. Hg, and, because of the likelihood of cerebral anoxia during the initial episode, I injected 30 ml. of 50% sucrose intravenously at 8 P.M. The patient then suddenly stopped breathing and turned greyish-blue; his pupils dilated; and his pulse became impalpable. Within 30 seconds the surgeon arrived in the ward and reopened the chest wound, while I began mouth-to-mouth expired-air inflation. The apex of the heart had herniated through the gap in the pericardium as far as the atrioventricular junction, which was marked by a constriction ring. The ventricles were fibrillating. The surgeon incised the pericardium down to the diaphragm and began cardiac massage, while ventilation was continued by mouth-to-mouth inflation for 3 or 4 minutes and was then maintained with air using an 'Ambu' resuscitator (Ruben and Ruben 1957) for about 10 minutes. When an anæsthetic machine arrived from the operating-theatre I passed an endotracheal tube and inflated the lungs with oxygen. As soon as cardiac massage had been started the patient's colour improved slightly and his pupils became less dilated, but ventricular fibrillation continued. One shock from a defibrillator had no effect, but three shocks in rapid succession restored normal rhythm. The total period of cardiac massage was 25 minutes. The chest was closed, leaving the pericardium widely open. By the time the skin had been sutured the blood-pressure was 110/60 mm. Hg and the breathing was deep and regular: an airway was not tolerated after the endotracheal tube was withdrawn. 40 ml. of 50% sucrose solution was given intravenously at 9.30 P.M. and again at 1 A.M. The patient began to recover consciousness at 2 A.M. and was fully conscious, though slightly irrational, by 9 A.M., 13 hours after the cardiac arrest. The systolic blood-pressure repeatedly fell to 80 mm. Hg on the first postoperative day, and paralytic ileus lasted for 24 hours. Recovery was otherwise uneventful: the wound healed well, and the patient's mental state seemed normal after about a week. He was discharged on the 18th postoperative day.

Discussion

In retrospect, there is little doubt that the heart herniated at the time of the first hypotensive incident (7 P.M.). In 7 out of 9 reported cases herniation was accompanied by shock, usually with an imperceptible pulse and a blood-pressure that could not be measured. 6 cases recovered: all 6 were explored while still in the operating-theatre, when the heart was found to be beating rapidly but feebly. 3 died 18–31 hours after operation, probably from obstruction of the great veins. Ventricular fibrillation has not previously been recorded, though it is a not surprising sequel.

Though a few successful cases of cardiac massage outside the operating-theatre have been reported—e.g., Beck et al. (1956), Clemetson (1959), and Walton (1960)—it is so often a forlorn hope that some workers (Carter et al. 1959) believe that it should not even be attempted. The present case shows that it can be life-saving, despite the handicap of a pneumonectomy, and that inflation with air can be a useful emergency measure. The circumstances which most contributed to the successful outcome were the arrival of two doctors within 30 seconds of the cardiac arrest, and a simple thoracotomy set which was kept in the ward.

The set consists of a small metal box containing a scalpel, scissors, toothed forceps, thread, two swabs, and a simple rack-and-pinion (modified Tuffier's) ribspreader. At the North Middlesex Hospital these sets are distributed to the thoracic surgical wards, the X-ray department, and the electroconvulsive-therapy department. An 'Ambu' resuscitator (or its equivalent) is kept with each set; this allows efficient pulmonary ventilation to be started without waiting for an anæsthetic machine and endotracheal tube.

This experience has convinced me that such simple thoracotomy sets and air resuscitators of expanding-bag or bellows type should be provided in every surgical ward. Even though it will often be impossible to find a doctor promptly, such a precaution seems well worth taking, since the cause of the cardiac arrest may be removable and recovery may be possible with prompt treatment.

Summary

In a case of cardiac herniation after intrapericardial pneumonectomy, causing ventricular fibrillation, successful resuscitation was helped by an emergency thoracotomy set and a bellows-type respirator which were available in the ward.

I am grateful to Mr. M. Bates for permission to publish this case and for helpful criticism, and to Mr. R. L. Hurt and Dr. G. S. A. Knowles for their advice. The ribspreader described here was designed at St. Bartholomew's Hospital, London, and is made by Heaton, Grogon & Co., Ltd., 21, Bowling Green Lane, London, E.C.1.

References overleaf

* Present address: The London Hospital, London, E.1.

New Inventions

A MEDICAL METERING PUMP

THERE are many purposes for which accurate doses of liquids have to be given over long periods. These include:

1. Tube-feeding of high-protein/high-calorie diets in malnourished patients; the conventional drip-feed requires constant attention and may result in variations in flow that lead to diarrhœa.

2. Constant-infusion techniques in renal-function studies, particularly in children in whom variations in rate of flow are more critical than in adults.

3. Infusion of packed red blood-cells to infants, when slow rates are very difficult to achieve because of the physical characteristics of gravity-infusion equipment.[1]

4. Metering of accurate doses of anticoagulant and antagonist to produce regional effects on blood-clotting in such equipment as the artificial kidney.

5. Administration of very viscous liquids, such as triple-strength plasma.

Though special equipment for most of these purposes has been designed [2–6] there is need for a simple, accurate, all-purpose pump which satisfies the criteria for use under sterile and non-sterile conditions. Such a pump should be easy to clean, and have a minimum of moving parts in contact with the liquid to be administered; preferably, its head should be sterilisable by dry heat. In addition the pump should be highly reliable, noiseless, easily adjusted, and have a reasonably wide range of accurately adjustable rates of flow.

Metering pumps meeting some of these requirements have been used for many years in industry, and the pump described

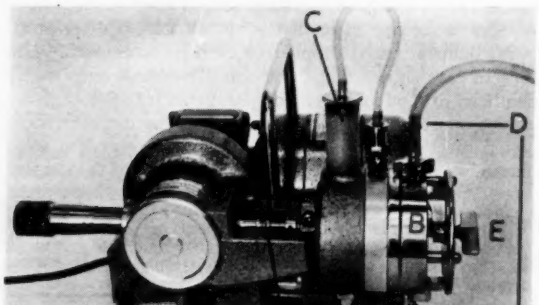

Fig. 1—The modified metering pump (explanation of letters in text).

here has been adapted from an industrial design. The liquid is propelled by an accurately machined piston, the travel of which is varied by a micrometer screw. This piston reciprocates in contact with a chamber containing ball-valves to control the direction of flow. This system produces a pulsatile output, but the volume of each pulse is so small that flow is virtually continuous through cannulæ or indwelling needles.

Initial experience with an industrial pump showed that the apparatus was satisfactory in principle for clinical use. Though the direct contact between piston and liquid was acceptable for non-sterile liquids, it could not be tolerated for sterile

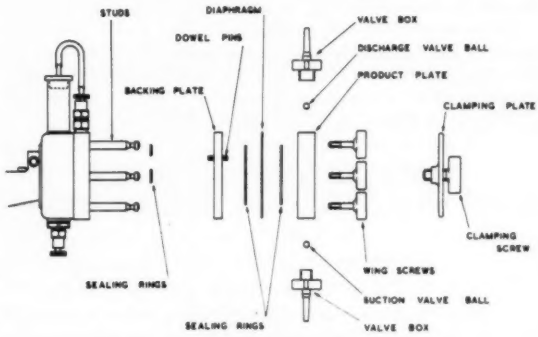

Fig. 2—Exploded diagram of pump head.

liquids; and, in addition, the gland packing in the piston chamber sometimes gave trouble. The pump head was therefore modified to provide an isolated pumping system.

The pump (fig. 1) is driven by a geared electric motor. The piston (A) actuates a closed hydraulic system which is in contact with the pump head (B); and the level of water in this system is visible in a transparent chamber (C). The pump head (fig. 2) consists of an 0·5 mm. (0·015 in.) polytetrafluoroethylene (' Fluon ', I.C.I.) disc in contact on one side with a chanelled product-plate and on the other with the hydraulic system. The direction of flow is controlled by two ball-valves accessible through the inflow and outflow connections (D) in the product-plate. These connections can be removed by hand. Flow is produced by flexion of the disc in response to pressure change in the hydraulic system induced by the action of the piston. The head of the pump is held together by three wing screws and can be dry-sterilised in a hot-air oven. It is secured to the hydraulic system by a clamping plate with a single wing screw (E); location pins prevent misalignment.

The fluon discs are chemically inert and extremely tough; they have already been tested to many thousands of hours' use without showing any sign of wear. Even if a disc should rupture the pump " fails safe " and ceases delivery. The pump is set so that, if a pressure of 400 mm. Hg develops in the outflow line, the hydraulic system cycles, flow ceases, and a dangerous increase of pressure on the delivery side of the pump cannot take place. This apparently high pressure is necessary because with a very fine needle, such as is used for pædiatric infusions, pressure in the tubing may be as high as 100 mm. Hg. Because the pump can cycle, the outflow line may be clipped off without stopping the motor. Most of the mechanical parts of the pump are of magnesium alloy, and it weighs about 18 lb.

The flow-rate of the pump is continuously variable from 0 to 1 litre per hour. The scale on the micrometer screw reads from 1 to 10, corresponding roughly to increments of 100 ml. When great accuracy is essential, individual calibration is recommended, and is possible to within 2 ml. per hour.

Air can only gain access to the circuit if any part of it is at less than atmospheric pressure, or if the source of liquid is exhausted. The former difficulty is overcome by having both the supply flask and the patient above the pump so that there are positive pressures on the inflow and outflow sides. If air is drawn into the pumping chamber the volume of this is small enough for the air to expand and contract against the head of remaining fluid during the pump's cycle: entry into the delivery side then stops. A time-switch can be added to the motor to arrest delivery before the source runs dry.

Prototype pumps have now been in use for over a year for tube-feeding of special liquid diets and blended whole food, for metering inulin in renal-function tests, and for the infusion of packed red blood-cells in infants. In the last application, slight hæmolysis was found after the recycling of stored blood

1. Walton, J. N. *Lancet*, 1947, i, 662.
2. Last, C. E. *Brit. med. J.* 1945, i, 122.
3. Snyder, C. C. *Plast. reconstr. Surg.* 1951, **8**, 73.
4. Joseph, M., Schnieden, H. *Lancet*, 1955, i, 122.
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for 16 hours. By the method of Hunter et al.[7] 0·008% of the circulating hæmoglobin was found in the plasma after one passage of the blood through the pump. When blood has been pumped, thorough cleansing (as for cardiac catheters) is necessary to avoid reactions on further infusions.

Mechanical failure has not taken place, and in the more recent designs even viscous liquids—such as triple-strength plasma and thick suspensions—have been readily given.

We are most grateful to Mr. T. B. Philip and his colleagues of the Distillers Company, Ltd., Epsom, Surrey, for the development of these pumps.

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Medical Societies

MANCHESTER MEDICAL SOCIETY

Cardio-œsophageal Junction

AT a meeting of the Section of Anæsthetics on Feb. 16, Dr. J. GREENAN discussed the Cardio-œsophageal Junction.

Dr. Greenan said that changes in the position of the stomach altered the competence of the junction. He described observations on 18 patients who underwent laparotomy under general anæsthesia, and in whom the intragastric pressure was measured and the competence of the junction was investigated in three positions: (*a*) in the normal undisturbed position, (*b*) with the stomach displaced upwards and to the left to make the œsophagofundal angle more acute, and (*c*) when the greater curve was drawn down to make this angle more oblique.

In 16 cases upward displacement of the stomach, which made the œsophagofundal angle more acute, increased the competence of the junction. Downward traction on the stomach made the sphincter considerably less competent than in the undisturbed position of the stomach. In the last 2 cases, in 1 of which a sliding hiatus hernia was suspected preoperatively, a lax hiatus was demonstrated at operation. Upward displacement of the stomach in these cases caused part of the stomach to slide up into the hiatus, making the œsophagofundal angle less acute and the cardio-œsophageal junction less competent.

Despite general anæsthesia the nerve-supply to the part was shown to be functionally intact by: (1) administration of promethazine only as premedication and the subsequent necessity of coping with the excessive salivation when a potent vagolytic drug was not employed; (2) stimulation of the vagus by a circular electrode over the lower œsophagus, which consistently led to distinct peristalsis accompanied by a rise in intragastric pressure of the order of 4–7 cm. of water. After division of the vagus nerve further stimulation failed to produce peristalsis or a rise in intragastric pressure. This showed that nerve stimulation, and not stimulation of the underlying œsophageal wall, was responsible for the previous rise in pressure. Thus, at the time of the investigation on the competence of the cardio-œsophageal junction, the motor nerve-supply to the part was functionally intact.

The competence of the junction varied with different positions of the stomach, and the trend observed was identical with that observed by Marchand in his work on cadavers.

7. Hunter, F. T., Grove-Rasmussen, M., Soutter, L. *Amer. J. clin. Path.* 1950, **20**, 429.

Reviews of Books

Recent Advances in Tropical Medicine

3rd ed. Sir NEIL HAMILTON FAIRLEY, K.B.E., M.D., F.R.C.P., F.R.S., consulting physician, Hospital for Tropical Diseases (University College Hospital), London; A. W. WOODRUFF, M.D., PH.D., F.R.C.P., Wellcome professor of clinical tropical medicine, University of London; JOHN H. WALTERS, M.D., F.R.C.P., physician, Hospital for Tropical Diseases (University College Hospital), London. London: J. & A. Churchill. 1961. Pp. 480. 50*s*.

THIS volume is completely new, for it has been entirely rewritten and is not a revision of the 2nd edition (now 32 years old). It therefore covers a time during which more advances have been made in treatment and control of tropical diseases than in any comparable period, though the advances may not have been so fundamental as in the great Manson epoch; and it concentrates on the past decade.

It is an excellent book, well and carefully conceived to link present knowledge with past experience, and the authority of the contributors is evident. They cover most of the important protozoal, helminthic (but not *Brugia malayi* infection), bacterial (including the enteric fevers and brucellosis), and spirochætal diseases, the virus and rickettsial diseases, fungal diseases, short-term fevers, venereal diseases, nutritional diseases and anæmias, some hereditary disorders (hæmoglobinopathies and kuru), and some diseases of uncertain origin. There is a good index.

The emphasis is on clinical aspects and treatment, and, though there are many short sections on epidemiology, pathology, and control, it is a book for the practising physician rather than the public-health officer. It is also a book to which the medical administrator should often turn for a picture of modern trends and needs.

Much literature is quoted, and in many places the authors state without comment what others have written, leaving the reader to judge for himself. This is inevitable over so wide a range, but in those many instances where the authors give a lead in evaluating work reported, there is a refreshing vigour of thought and practice. A number of spelling mistakes—for example Cardon for Corson (p. 22), Sandoshan for Sandosham (p. 164), *Ferrisia tenius* for *Ferrissia tenuis* (p. 143, where the mode of experimental infection is confused, and the reference is incorrect)—are minor blemishes on a notable contribution to an important and fascinating subject.

Hysteria: Reflex and Instinct

ERNST KRETSCHMER, M.D. Translated from the German by VLASTA and WADE BASKIN. London: Peter Owen. 1961. Pp. 162. 30*s*.

Professor Kretschmer's little book has gone through many German editions (the publishers do not say which this is) and will arouse wide interest. It is a philosophical treatise rather than a description of the disorder, and little account is taken of views other than the author's; nor does it help in treatment. But his biological approach is stimulating: like the animal, the hysteric faced with danger displays a flurry of instinctual "escape" activity (panic, fugues, and convulsions) or an "autohypnoid" death feint (stupor, mutism). A third category of hysterical features grafted on to brief illness or injury has the similar phylogenetic purpose of protection from danger. Here, indeed, is a concept of regression.

Kretschmer's theoretical personality structure seems of less relevance than that of Freud (many of whose concepts are shared) though admittedly the clinical facts fit better Kretschmer's belief that sex and self-preservation play equal parts in genesis of hysteria. But his account of "hypobulic" and "hyponoic" mechanisms interposed between the conscious purposive will and the reflex level, must remain of doubtful help. This study originated in the disorders of 1914–18, and cases (of multiple personality, for example) could be put forward which fit the theory less well. Hysteria and "dissociation" are, diagnostically, coming to mean either everything or nothing: here, for example, we find a great many psychopathic reactions

included, but when the book refers on p. 51 to " cyclic hysterics, such as schizophrenics and epileptics " the translation is at fault. Elsewhere, " characterological stigmatization " seems only to mean personality. Emphasis is placed on constitutional factors—no surprise in view of the author's classic work on personality and physique (though hysteria does not fit into his somatotype scheme)—and perhaps we have paid too little attention to the work mentioned here, correlating psychological and physical immaturity.

At a time when hysteria is under critical re-examination, even to the point of doubting its existence as an entity, this important treatise is opportune. The Continental didactic tradition does not appeal to everyone, but the book is well worth careful study.

The Chemistry of Thyroid Disease

ROSALIND PITT-RIVERS, M.SC., PH.D., F.R.S., JAMSHED R. TATA, M.SC., D. ÈS SC., National Institute for Medical Research, London. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 83. 36*s*.

The Thyroid Hormones, by the same authors, gave a comprehensive account of the biochemistry of the normal thyroid, and this book supplements the larger volume by describing some of the biochemical findings in patients with hypothyroidism, hyperthyroidism, and thyroid cancer. Since immunology can be considered a branch of protein chemistry, a chapter has been included which ably reviews recent events in this area. This book will be extremely useful to those clinicians who want to bring their knowledge of the biochemistry of thyroid disease up to date; but for a comprehensive account of, for instance, the metabolic consequences of hyperthyroidism or hypothyroidism they must turn to older textbooks. As an example of the emphasis on recent advances, no less than 16% of the entire text is devoted to an excellent review of the nature of the elusive " compound X ", found in the serum of some patients with thyroid cancer. The book should, therefore, be regarded as a collection of able and well-balanced reviews of the growing-points of research in this field, rather than the comprehensive textbook which the title suggests.

The Ethics of Medical Practice

JOHN MARSHALL, M.D., F.R.C.P.E., M.R.C.P., D.P.M., reader in clinical neurology, University of London. London: Darton, Longman & Todd. 1960. Pp. 164. 21*s*.

EVER since he ate the fruit of the tree and knew good and evil, ethical problems have been part of Man's daily lot. Doctors have a full and increasing share, and no doubt they are ready to welcome whatever help books may give so long as their consciences remain free for consultation. In its more general chapters and especially in its informed and lucid presentation of problems that may suddenly confront them, this book will provoke thought and, within limits, help; but, though the title does not say so, it is in fact an exposition of medical ethics for Roman Catholics. Others, including many who " profess and call themselves Christians ", will find themselves forced to take a quite opposite view of right and wrong and of the doctor's duty in many of the situations cited, and they may feel that something warmer than the intellectual arguments here adduced should determine their conduct. The ordinary practitioner may also think that 60 pages (out of 160) on matters arising from reproduction, with hardly a mention of examination, certification, and reference to hospital, which, in actual fact, give his conscience its " daily dozen ", argues a certain failure in sense of proportion. For Catholics, for whom it is really written, the book can be confidently recommended.

Toxicology and Biochemistry of the Aromatic Hydrocarbons

H. W. GERARDE, M.D., PH.D., toxicologist, Esso Research and Engineering Co., New Jersey. Amsterdam: Elsevier Publishing Co. 1960. Pp. 329. 30*s*.

THE aromatic hydrocarbons are among the most widely used chemicals in industry, and from them are derived such diverse products as aviation fuel, dyestuffs, drugs, and insecticides. Many of them, particularly those with a comparatively small molecule, are toxic on ingestion or inhalation; others, even those of high molecular weight, can cause dermatitis.

This book, one of a series on toxic agents, is written primarily for factory medical officers; hence, the toxic effects of drugs and insecticides with a benzene-ring structure are not discussed. The first section is an introduction to the nomenclature and structure of the aromatic hydrocarbons, and also deals with the toxicological and biochemical features they have in common.

Twenty of the most important " aromatics " are treated in detail, with particular reference to their biological hazards and maximum admissible concentrations in the atmosphere, which are practically the same as those adopted in this country. The use of the American billion is a trap for the unwary—index notation would be less likely to lead to confusion.

A chapter is devoted to the carcinogenic polycyclic hydrocarbons, and the state of present knowledge is reviewed concisely but thoroughly. There is no mention, however, of the possible association between the benzpyrenes or the benzanthracenes and bronchial carcinoma.

The references are not confined to American sources and are complete to the end of 1959; in addition, much original unpublished work is mentioned.

The paper and printing are good, but the structural formulæ and some of the illustrations are rather small, and the paperback binding seems a little fragile for such a useful reference book. The text is easy to read and is enlivened by some entertaining " asides ".

Facing Retirement

A Guide to the Middle Aged and Elderly. London: Allen & Unwin. 1960. Pp. 111. 12*s*. 6*d*.

THIS wise and thoughtful book, written anonymously by " A Country Doctor ", is a guide to those who are sensible enough to give forethought to the problems of their old age. The subjects include the finances of retirement, with special reference to pensions and national assistance, the disposal of capital, and the making of wills. Wise advice is given on whether to live alone or with relatives, and how to do so harmoniously. There are chapters on the preservation of health, including sight and hearing, and the place of religion in adjustment to old age. The book begins with a lively foreword by a distinguished nonagenarian and ends with a postscript from the same hand.

The writing is clear and simple, but coloured by a profound insight into human problems and relationships, suggesting the conversation of an ideal family doctor—humane, kindly, practical, clear-headed, and well informed. Perhaps only the traditional system of general practice could have produced a book like this, and we hope the author will write more, perhaps under his own name.

This book could certainly be read with profit by all people facing retirement, and it will also be very valuable to their younger relations and to doctors who want to help them to the full.

Illustrating Medicine and Surgery

MARGARET C. MCLARTY, D.A. Edin., founder member, Medical Artists' Association of Great Britain, and artist, United Oxford Hospitals. Edinburgh: E. & S. Livingstone. 1960. Pp. 159. 37*s*. 6*d*.

ONE of the first in this country to recognise the value of a trained medical artist was Sir Hugh Cairns, who, soon after he was appointed assistant surgeon to The London Hospital, sent a member of his staff to study under Max Brodell at Baltimore. It is apt then that this new textbook, one of the first on its subject printed in Britain, should come from the centre where Cairns later worked.

Its chief readers will be art students aspiring to a career in this specialty. But any physician and surgeon contemplating a paper or a lecture involving some illustration of his material would do well to examine this book. He is likely to use his illustrations to better advantage if he is aware of their limitations and possibilities. The book is itself illustrated with a variety and elegance that make it a delight.

THE LANCET

LONDON 25 MARCH 1961

Hospital Doctors

The report of the Working Party on Medical Staffing Structure in the Hospital Service (summarised on p. 657) contains a useful analysis of present deficiencies and makes a number of constructive suggestions. Its plans for bringing many more general practitioners into hospital work represent an important advance, and its other proposals should overcome some of the present difficulties of staffiing hospitals. Whether they go far enough is another matter.

The deficiencies in the existing structure are of two sorts: first, there are not nearly enough doctors below the level of consultant; and, secondly, there is a lesser shortage of consultants themselves. These deficiencies, and any alteration of the structure, need to be considered in relation to changes in hospital practice—notably the larger demand on outpatient departments, the changing pressure on the different inpatient departments, and a trend towards professional team-work. In our view the working party does not take enough account of this evolution.

The report rejects the establishment of a specialist grade immediately below that of consultant, and it does not explicitly accept the alternative plan by which the consultant grade would be enlarged to cover all who may be regarded as fully trained specialists. "All patients in the Hospital Service", it says, "should be in the charge of consultants"; and "Doctors below consultant rank should act as assistants to the consultants ..." Its main recommendation for increasing the assistance to consultants is that a new career grade with the generic title of "medical assistant" be established. Appointments to this grade would be open to senior registrars, registrars, or general practitioners, subject to the candidate having worked for at least two years as a registrar. This grade would be at a lower level than the specialist grade which we ourselves have advocated; and, since it would not be an obligatory step on the way to consultant rank, it would often seem a step downwards for those with consultant aspirations. If this grade entitled a doctor to be called "assistant physician" or "assistant surgeon", it would be more attractive; but the working party rules this out because some hospitals at present use "assistant physician" for a full consultant. The proposed names of "assistant in surgery", "assistant in chest medicine", and so on—with their hint of incomplete qualification—would we fear be a deterrent rather than an inducement. Nor is the grouping in one grade of those with widely differing length of experience likely to attract the more senior. The work of a "medical assistant" is to be roughly that of a registrar. Will a senior registrar who has served in that grade for four or five years be content to revert to registrar level? The very fact that a senior registrar has been retained in a post for four years should indicate that he is a strong candidate for a consultancy. Appointment to consultant posts is, rightly, competitive; but failure to win such a post is by no means always due to unsatisfactory professional skill. We still believe that the hospital service should fully exploit the experience of those who do fail in this way. The working party seems to be persuaded that under its scheme it will be doing this; for it denies that "there is a class of medical work which may be called 'senior registrar work'". Many senior registrars would concur: often senior-registrar work is consultant work; and those who have done such work will not readily enter the amorphous "medical assistant" group.

Nor does the report seem wholly satisfactory in its survey of the organisation of consultant services. "Outpatient arrangements", it says, "should be such that junior staff are not left in sole charge, except in the occasional unavoidable absence of the consultant." But, as it admits, under existing circumstances some senior registrars see outpatients almost routinely. Furthermore the pressure on outpatient departments is growing; and we should surely encourage this trend, whereby more patients are treated without admission to hospital, and more of those who eventually are admitted are first investigated as fully as possible. But an outpatient service can be effective only if the patients are seen without delay; and at present delays of weeks are not uncommon. Would it not be realistic to remedy this defect by appointing time-expired senior registrars as assistant physicians or assistant surgeons to do this and other clinical work? If a specialist grade is still unacceptable, should they not be appointed as junior members of the consultant grade, extended for the purpose? If this were the normal way of promotion, they could hope to gain senior consultant status; or, if they failed to move up that particular ladder, they would at any rate have the assurance of a satisfactory career. The working party shows awareness of the crying needs of outpatient departments when it speaks of the appointment of an additional consultant where there is no scope for one "with responsibility for a substantial proportion of the beds". In such circumstances an additional consultant might be employed as the junior partner of a firm; but "he should always be given some beds as of right". This is a crucial point: inability to find the beds a consultant expects has quite often prevented the appointment of one to undertake much-needed outpatient work.

We wish the working party had taken this opportunity to dispel the prevalent respect for number of beds as the clinical consultant's status symbol. Likewise it could perhaps have shown greater flexibility in its approach to the division of beds. It does press for wider

adoption of the "firm" system; and of the interchange of beds it says:

> "... beds could be allocated in specific numbers to each firm or each consultant, but firms on emergency duty could 'borrow' beds from other firms when needed or a medical firm borrow from a surgical firm or vice versa."

This is admirable as far as it goes, but it does not really solve the problem of the consultant who clings to beds which (temporarily or otherwise) are needed more by other departments around him. Nor does the report hint at the emerging truth that allocation of beds to particular consultants or particular specialties is becoming outmoded by the healthy growth of team-work.

These comments concern the work of hospitals, rather than staffing structure. But before staffing can be rationally settled, the work must be defined. In truth the working party's account is the second part of a report whose first part—on the character and volume of medical work in present-day hospitals—has yet to be commissioned.

Biochemical Individuality

THE concept that human beings differ from one another in the details of their biochemical make-up, that such differences are often genetically determined, and that each person probably has a unique biochemical constitution or individuality was first clearly stated by A. E. GARROD in 1902.[1] He arrived at this view from a consideration of the biological significance of a series of rather rare abnormalities such as alkaptonuria, albinism, and cystinuria, which he later christened "the inborn errors of metabolism". He suggested that these conditions were simply extreme and rather striking examples of biochemical variations which were, as he put it, "probably everywhere present in minor degrees". He concluded that "just as no two individuals of a species are absolutely identical in bodily structure, neither are their chemical processes carried out on exactly the same lines". Such subtle chemical differences between healthy human beings were first demonstrated by LANDSTEINER[2] in his fundamental work on the ABO blood-groups, the first results of which were published at about the same time as were GARROD's. LANDSTEINER showed that people could be classified into distinct types according to whether they possessed one (A), another (B), both (AB), or neither (O) of two different antigenic substances on the surfaces of their red blood-cells. The differences in the immunological properties of these substances implied differences in their chemical structures, and these differences were soon found to be genetically determined.

Since then, a series of other genetically determined systems of red-cell antigens, such as the MNS system and the Rh system, have been discovered. In general each system is determined independently of the others, so that any individual has, on the surface of his red cells, a complex of antigenic substances which includes components belonging to each of these different systems. By using all the antisera which are available to characterise these different red-cell antigens, it is now possible to define several million different classes of people according to the combination of these antigenic substances on their red cells. Many of the combinations are very rare; but the discriminating power of these techniques is illustrated by the findings of RACE and his colleagues,[3] who in 1950, using 17 of the different antisera then available, were able to classify 475 Londoners into 296 distinct types. Of these 296 antigenic combinations 211 occurred only once, and no more than 10 individuals had the same combination. No doubt an even more dramatic result would be obtained if all the blood-group antisera available today were used in this way. At any rate these findings afford some measure of the individual differentiation in respect of what is only one feature of the body's biochemical architecture.

Because of the sensitivity and elegant simplicity of the techniques at their disposal, blood-group workers have long led the field in characterising and defining in precise terms the material basis of human individuality. In the last few years, however, the subject has begun to develop in new directions. For example, it has been found by starch-gel electrophoresis that people can be classified quite sharply into several distinct types according to the character of their haptoglobins—a group of proteins which are normally present in blood-serum.[4] Other examples of serum-protein variations which have been recently discovered include the transferrin types,[4] also detected by starch-gel electrophoresis; the γ-globulin types,[5] identified serologically; the serum-cholinesterase types,[6] determined enzymatically; and the α_1 Gc types,[7] recognised by immunoelectrophoresis. Each of these variations is genetically determined, and each serves to classify human beings into two or more distinct groups.

In this issue Dr. ALLISON and Dr. BLUMBERG report from Mill Hill a further example of human biochemical polymorphism. These workers investigated the possibility that in sera of people who had received many blood-transfusions there might be antibodies which would react with particular serum-proteins, present in some individuals but not in others. They succeeded in finding one antiserum which gave a precipitin reaction with what appeared to be an α_2 macroglobulin. This α_2 component was present in about half the population of white and Negro Americans tested, and family studies showed that its presence or absence was genetically determined. Evidently the genes concerned here, like those determining many other well-known instances of polymorphism, occur with widely different frequencies in different populations, because in a sample of Micronesians 50 out of 51 individuals gave a positive precipitin reaction.

Specific biochemical differences of this sort are of obvious interest to both geneticists and biochemists. Possibly, too, they may prove of practical significance in

1. Garrod, A. E. *Lancet*, 1902, ii, 1616.
2. Landsteiner, K. *Wien. klin. Wschr.* 1901, **14**, 132.
3. Bertinshaw, D., Lawler, S. D., Holt, H. A., Birman, B. H., Race, R. R. *Ann. Eugen., Lond.* 1950, **15**, 234.
4. Smithies, O., Connell, G. E. *Biochem. J.* 1959, **72**, 115.
5. Grubb, R. *Vox sang.* 1957, **2**, 305.
6. Kalow, W. *in* Ciba Foundation Symposium on Biochemistry of Human Genetics (edited by G. E. W. Wolstenholme and C. O'Connor). London, 1959.
7. Hirschfeld, J., Beckman, L. *Acta genet.* 1960, **10**, 48.

medicine. The more extensive our knowledge of the differences in biochemical make-up between different normal individuals becomes, the more likely are we to begin to understand why people react differently from one another in similar environments, and why some people are more susceptible than others to particular types of clinical disorder. The idea of diathesis is an old one in medicine, but it has always been nebulous. Studies of the sort discussed here may in the future provide a firm scientific basis for this old-established belief.

Varieties of Alcoholism

WHAT is alcoholism? When ten years ago the World Health Organisation's Alcoholism Subcommittee held its first session it suggested as an "ad hoc and provisional" definition "any form of drinking which in its extent goes beyond the traditional and customary 'dietary' use, or the ordinary compliance with the social drinking customs of the whole community concerned, irrespective of the ætiological factors leading to such behaviour and irrespective also of the extent to which such ætiological factors are dependent upon heredity, constitution or acquired physiopathological and metabolic influences".[1] A year later, at its second session, the subcommittee considered it "more appropriate to use the preceding definition to define the term 'excessive drinking'". It now defined alcoholics as "those excessive drinkers whose dependence upon alcohol has attained such a degree that it shows a noticeable mental disturbance or an interference with their bodily and mental health, their inter-personal relations, and their smooth social and economic functioning; or who show the prodromal signs of such developments. They therefore require treatment."[2] The subcommittee went on to distinguish two categories of alcoholics: the "habitual symptomatic excessive drinkers" or "non-addictive alcoholics", and the "addictive drinkers" or "alcohol addicts". The main difference between these two categories consists, as E. M. JELLINEK explained in an appendix to the report, in the occurrence only among alcohol addicts of loss of control over alcohol intake after several years of excessive drinking. Loss of control indicates the onset of the third or crucial phase in the development of addiction, resulting in further drinking until the point of intoxication or sickness. JELLINEK felt that, "strictly speaking, the disease conception attaches to the alcohol addicts only, but not to the habitual symptomatic excessive drinkers".[2]

Two years later a W.H.O. Expert Committee on Alcohol and Alcoholism concluded that there was, besides loss of control, another criterion that might serve to distinguish "true" alcoholism—i.e., "inability to stop drinking."[3] Whereas loss of control was found chiefly in predominantly spirit-drinking countries—such as the U.S.A.—inability to stop drinking was more characteristic of alcoholism in predominantly wine-drinking countries, such as France: the drinker taking alcohol day-in, day-out, from morning till night without necessarily (or even generally) getting drunk. Each of these two drinking patterns could be found in all countries, but often with one so much the commoner that the other might be overlooked. And, as JELLINEK later pointed out,[4] "in many countries problems of national magnitude arise more from other types of drinkers than from the steady excessive symptomatic drinkers with or without addictive features". The problem of alcoholism seems to vary from country to country.

JELLINEK, whose work has been mainly responsible for clarification and progress on this complex issue, has summed up his present views.[5] Alcoholism, he now concludes, is not a specific but a generic term. It is a fairly broad genus with a large number of species, the various alcoholisms described in different countries having only two features in common—drinking, and the damage (to individual and/or society) resulting from it. The genus can therefore be defined only vaguely; but taking into account ætiology, elements of the alcoholic process, and type of damage, JELLINEK tabulates five of the most common species of alcoholism, which he calls by the first letters of the Greek alphabet.

As regards ætiology, psychological vulnerability, varying from slight psychological deficits to outright neurosis or psychosis, is present in all species. The role of physiological vulnerability is hypothetical: physiopathological elements may possibly be important in the development of the addictive process. Finally sociocultural elements, such as the attitude towards drinking and drunkenness, and economic elements, among them the price of alcoholic drinks, play varying parts in the different species.

Among the elements of the alcoholic process, JELLINEK considers first acquired increase of tissue tolerance: this is present to a slight extent in all regular drinkers, but its rapid development to a high degree may be a major element in the process of addiction—that is, physical dependence. JELLINEK discusses the main addictive features—i.e., besides acquired increased tissue tolerance, an increase of the dose, withdrawal symptoms, and craving. The addictive process is coupled either with loss of control with unimpaired ability to abstain after a bout or with inability to abstain even for twenty-four hours but without loss of control over the amounts ingested. Dependence in the various species of alcoholism may be psychological or physical—though in certain species there is neither, but instead dependence on social custom such as heavy weekend drinking. Nutritional and physical habits may greatly contribute to the damage in some species.

Alcoholism is usually described as a progressive condition, but JELLINEK points out that only in the two true addictive species of alcoholism is there progression from social drinking over various stages[2] to eventual loss of control and/or inability to abstain. In other species of alcoholism progress consists merely in the development of manifestations of chronic alcoholism.

1. Expert Committee on Mental Health. *Tech. Rep. Ser. Wld Hlth Org.* 1951, no. 42, pp. 5, 19, 20, 21.
2. Expert Committee on Mental Health. *ibid.* 1952, no. 48, pp. 16, 26, 33, 38.
3. Alcohol and Alcoholism: report of an expert committee. *ibid.* 1955, no. 94, p. 7.
4. Jellinek, E. M. *World Health, Geneva*, 1957, **10**, 4.
5. Jellinek, E. M. *Canad. med. Ass. J.* 1960, **83**, 1341.

Only the first two species, representing addiction in the strict pharmacological sense, and termed " gamma " alcoholism (involving loss of control) and " delta " alcoholism (inability to abstain) are regarded by JELLINEK as diseases. Two other species (" alpha " and " epsilon " alcoholism) may be symptoms of underlying disorders. Finally, " beta " alcoholism results from certain cultural drinking patterns, which in conjunction with poor nutritional and physical habits are responsible for the development of complications (chronic alcoholism) and is neither a disease nor a symptom of a disease.

Delta alcoholics predominate in France, gamma alcoholics in the U.S.A. As far as this country is concerned, published studies deal almost exclusively with the species now termed by JELLINEK gamma alcoholics; but GLATT's[6] work suggests that other types of alcoholics may not be very uncommon here. Some of JELLINEK's researches have greatly influenced work in this country. Thus the Jellinek formula, providing an estimate of the prevalence of chronic alcoholism, underlies the usual estimate of 86,000 chronic alcoholics in England and Wales,[1] and his concept of the developmental process of alcohol addiction [2] has been found by GLATT [7] to apply also to alcohol addicts in this country.

Annotations

EXCEPTIONAL CHILDREN

MANY families in this country contain exceptional children. Unfortunately some of them are exceptional because they are mentally or physically handicapped. Their need of help is recognised, and to some extent provision is made for their education. There are special schools, for instance, for backward children, deaf children, blind children, spastic children. There are some, though probably too few, residential places. No-one would dispute that these vulnerable children have a special claim on the community and that we still have not done enough for them. There is, however, it was lately suggested in the House of Commons, another, smaller, group of exceptional children whose needs are still unrecognised—children of outstanding intelligence in families where there is not money to provide special educational opportunities.

Last month on the adjournment Mr. Philip Holland [8] drew attention in the House of Commons to the difficulties of a father of limited means who had a 9-year-old son who was said to have an I.Q. of 171 whom he was anxious to send to a boarding-school with a high teacher/pupil ratio. Mr. Holland pointed out that the only provision in the State educational framework for exceptionally gifted children was a permissive regulation which allowed a local authority to make a grant out of its own funds. In view of the many claims on their resources, authorities could not be blamed for showing a certain reluctance to use these powers. But the country urgently needed first-class scientists, and he thought that we should no longer rely on " a passive permissive permission " to meet the needs of the " raw material in its earlier stage of development". If local authorities were reimbursed for any grants they gave to children of high intellectual calibre, they might be less inhibited in making contributions. The scope for help of this kind was shown by the reply of Mr. Kenneth Thompson, parliamentary secretary to the Ministry of Education. He said that there might be as many as 25,000 children in England and Wales in each age-group with an I.Q. of somewhere between 138 and 171. But he was uncertain about the wisdom of providing special schools for supernormal as well as subnormal children.

Perhaps neither the solution nor the problem emerged clearly from the debate, and a more helpful approach is to be found in Dr. C. O. Carter's suggestion,[9] based on surveys by the Eugenics Society of 250 families with at least one child of high intelligence. The surveys showed that more than a quarter of these families would have liked at least one more child and some would have liked several. As it was, they were a little below replacement-rate. The main obstacle to increasing the size of the family was lack of money. Dr. Carter believes that we are too apt to regard the amount of national talent as fixed, and in his view it would be a good investment actively to encourage our promising families to have more children (instead of rather ineffectually urging our problem families to have fewer). Four possible methods of population promotion are increased family allowances, increased educational grants, help with housing, and increased income-tax allowances for children. Of these, educational grants have Dr. Carter's support, for they could be used selectively to help to enlarge families of promise. He would like all children over sixteen judged suitable for full-time training to receive a grant sufficient to meet their living expenses. Part of the allowance would go to the mother to increase her ordinary family allowance, but Dr. Carter sensibly believes that it is important that part should go to the teenager, so that he does not feel that he is being a burden to hard-pressed parents or find himself at too great a disadvantage among his wage-earning contemporaries in the milk bar.

METHIONINE AND SCHIZOPHRENIA

SEVENTY-SEVEN years ago Thudichum [10] suggested that the psychoses resulted from production of abnormal chemical substances in the body; and he believed that the time would come when their production could be controlled. Unfortunately, the only real success has been in preventing the effects on the brain of excessive amounts of phenylethylamine—and then only if the diagnosis is made early in life. Diagnosis depends on the detection of phenylketonuria; and, as Jepson [11] has pointed out, by that time, though the amine can be inactivated rapidly, great cellular damage may have been done.

Many workers hope that further investigations into the effects of the hallucinogenic (or " psycholytic ") drugs, such as lysergic acid diethylamide, may throw some light on the mechanism of the psychoses, in particular of schizophrenia, and may suggest possible therapeutic methods. Results so far have been both conflicting and disappointing.[12]

A report from the United States on the action of *l*-methionine in schizophrenia, though not conclusive, indicates another approach. In a small but carefully designed study of 12 chronic schizophrenic patients,

6. Glatt, M. M. *J. clin. Pract.* 1961, **15**, 153.
7. Glatt, M. M. *Lancet*, 1959, ii, 397.
8. *Hansard*, Feb. 17, 1961, col. 1917.
9. Carter, C. O. *Eugen. Rev.* 1961, **52**, 197.
10. Thudichum, J. L. W. A Treatise on the Chemical Constitution of the Brain. London, 1884.
11. Jepson, J. B. *Times Sci. Rev.* 1961, no. 39; p. 18.
12. *Lancet*, Feb. 25, 1961, p. 444.

Pollin et al.[13] found that treatment with 20 mg. methionine per 70 kg. body-weight daily produced striking changes in the mental attitude of 4. These patients showed an increased flood of association of words and ideas, and had periods of increased insight. The changes disappeared as soon as the methionine was withdrawn, though the patients continued to receive a monoamineoxidase inhibitor (iproniazid). *l*-Tryptophan produced similar effects in other patients, but there was no overlap between the tryptophan and methionine reactors. Other aminoacids, including 5-hydroxytryptophan and *l*-dihydroxyphenylalanine (DOPA), did not alter behaviour in any way that could be detected clinically.

Whether the clinical changes represent a biochemically induced acute flare-up of a chronic schizophrenic process or a toxic delirium superimposed on it is still uncertain.

ACCIDENTS AT HOME

IN April, 1954, Aberdeen health and welfare department organised a home-safety week to focus public attention on the frequency of domestic accidents that were mainly preventable. Afterwards, district health visitors and others continued "quietly but persistently" to point out likely causes of accidents; group health education was developed extensively, and an illustrated booklet on home safety was distributed free at clinics and by health visitors. Although these measures were successful, it was clear that some home accidents could not yet be regarded as preventable; Dr. Macqueen, the city's medical officer of health, therefore applied to the Nuffield Provincial Hospitals Trust for a research grant to investigate domestic accidents.

Between Sept. 1, 1955, and Aug. 31, 1957, except during two holiday fortnights, the Aberdeen hospitals, 46 general practitioners, and over 60 health visitors informed the health and welfare department of 95% of the 4527 domestic accidents in the city (whose population in mid-1957 was 186,190) serious enough to received medical attention. 91·6% of notifications came from hospitals; 9·2% from health visitors (including 2·9% also notified from hospitals); and 2·1% from general practitioners (including 0·04% also notified from hospitals). A detailed investigation was taken of all reported: a specialist health visitor inquired about all accidents to old people, adults, and schoolchildren (about 64% of all accidents); and district health visitors investigated the rest (babies and children under school age).

The results[14] of the inquiries, which should be studied by all home-safety committees, show that 1898 accidents (41·9%) involved males and 2629 (58·1%) females. 55·6% of all accidents took place in pre-school and school children, who formed less than a quarter of the population, but only 8·3% in people aged 65 and over, who made up a tenth of the population.

There was no evidence to support the view that home accidents are commoner in winter than summer. Saturday was the worst day for accidents, particularly to schoolchildren and young adults, and was followed closely by Monday, when the elderly and middle-aged were mainly involved. The peak hours for accidents were 6–8 P.M., 10–12 A.M., and 2–4 P.M. Of the victims, 285 (6·3%) were admitted to hospital and 3967 (87·7%) received outpatient treatment. Each person at work was incapacitated for an average of just over 3 days; and the accidents that caused the highest average loss of working days and the highest percentage of cases with remaining disability were falls, scalds, and burns.

The findings of the survey seem to reflect the success of the local home-safety campaign. Other studies of domestic accidents treated in hospital as inpatients have generally yielded an incidence of 2–3 per 1000 population per year; in this inquiry the incidence of hospital-treated accidents was only 0·8 per 1000 population per year. Half the accidents were in the sixth of the population (children under 9 years) least capable of understanding and acting on reasoned argument, but, apart from falls, there were few accidents in old people.

Dr. Macqueen emphasises the important role of health visitors in the home and to a lesser extent of group health education, and he makes suggestions for future campaigns. Falls were common at all ages, but preventive efforts should be concentrated on women and on persons responsible for young children. Preventive measures against miscellaneous accidents (bruises, &c.) should be directed towards schoolchildren and women under 65; against cuts, burns, and scalds towards persons caring for young children, and towards girls and women up to 44; and against poisoning (other than by gas) towards persons responsible for young children.

DEATH DUE TO ANÆSTHESIA

DEATHS due to anæsthesia have engaged medical interest ever since Hannah Greener died under the influence of chloroform[1] soon after Sir James Young Simpson[2] had introduced this agent in 1847. It is now recognised, on the one hand, that death under anæsthesia is by no means always due to it, and, on the other hand, that death later is not always due to complications in the postoperative period, but may instead be due to something which the anæsthetist did or failed to do during the operation. In such circumstances it is no surprise that reliable information on deaths due to anæsthesia is difficult to obtain.

A single anæsthetist is unlikely to accumulate, even in a lifetime, enough clinical material for useful analysis; accordingly, committees have been established to study the subject. Their investigations, however, have two weaknesses. First, they can only formulate conclusions on the evidence before them, and they can rarely obtain additional information or elucidate matters of doubt. Secondly, they must—particularly if they are large committees—represent prevalent current opinion; and if the history of medicine teaches anything it is surely that prevalent current opinion is just as likely to be wrong as to be right. In this country the only committee which has made a serious contribution to the study of deaths under anæsthesia was that formed by the Association of Anæsthetists shortly after the 1939–45 war. Even that set itself only the limited objective of defining a number of causes of death due to anæsthesia[3 4]: it was unable to indicate the frequency of such accidents.

The idea of the study committee for deaths due to anæsthesia has taken root and flourished in the United States: indeed, no fewer than sixteen States have such commissions at work. The first of them reported as long

13. Pollin, W., Cardon, P. V., Jr., Kety, S. S. *Science*, 1961, **133**, 103.
14. A Study of Home Accidents in Aberdeen. By IAN A. G. MACQUEEN, M.D., D.P.H., medical officer of health, City of Aberdeen, and lecturer in public health, University of Aberdeen. Edinburgh: E. & S. Livingstone. 1960. Pp. 100. 12*s.* 6*d.*

1. See Armstrong Davison, M. H. *Brit. J. Anæsth.* 1958, **30**, 142.
2. Simpson, J. Y. *Lancet*, 1847, ii, 549.
3. Morton, H. J. V., Wylie, W. D. *Anæsthesia*, 1951, **6**, 190.
4. Edwards, G., Morton, H. J. V., Pask, E. A., Wylie, W. D. *ibid.* 1956, **11**, 194. See *Lancet*, 1956, ii, 80.

ago as 1951.[5] That in Baltimore has published its findings lately.[6] Because of the commission's composition and procedure, its findings may be to some extent vulnerable, but these are too striking to be ignored: anæsthesia was proved to be the principal cause of death in 6·3% of 1024 postoperative deaths and a contributory factor in a further 12·9%.

In this country official records indicate that the number of deaths due to anæsthesia has fallen year by year since 1938.[7] But such records are unsatisfactory; for sudden death due to anæsthesia rarely gives rise to specific postmortem findings, and the only person who is likely to know the cause of an anæsthetic death is the anæsthetist himself. It does seem, however, that there has been a true decline, partly owing to improvements in anæsthetic agents and techniques, and partly owing to the increase in specialist anæsthetists—notably since the start of the National Health Service in 1948. Nowadays the chloroform death is a thing of the past; the unexpected death of a more or less healthy patient undergoing a fairly minor operation is much less common than it used to be; deaths during thyroidectomy for toxic goitre, which some twenty years ago were all too common,[8] now seem to be rare; and even in emergency operative obstetrics an impartial inquiry has shown that the frequency of deaths due to anæsthesia has diminished.[9 10]

That deaths associated with anæsthesia are not still fewer is due to two main reasons. First, as anæsthesia has improved, so surgery has boldly extended its frontiers; and, secondly, every step forward in anæsthesia brings unexpected complications.

THE MEDICO-LEGAL SOCIETY

THE Medico-Legal Society celebrates its diamond jubilee this year. Founded in 1901, under the presidency of Sir William Collins, the society has furthered the knowledge of medicolegal affairs and has provided an institution where law and medicine meet on equal terms and to their mutual benefit. The presidential chair is occupied alternately by doctors and lawyers, and although it is with these two professions that the society is primarily concerned, its range of interests is wisely kept broad by including among its members any who have interest in forensic matters—scientists and police officers, for example. Regular meetings are held at which speakers, not necessarily members of the society, present papers on a great many medical, legal, and scientific topics. Valuable exchanges are likely between lawyers and doctors who may otherwise meet only in a strictly professional and often contentious arena.

The proceedings of the society are published in a journal originally entitled *Transactions of the Medico-Legal Society*, now known as the *Medico-Legal Journal*, whose contents are comprehensible to both lawyers and doctors, and from which very specialised or technical matters are excluded.

Newer medicolegal societies now exist in this country which, catering for the practising specialist, complement the more venerable Medico-Legal Society. Since its inception the society has favoured the establishment of a Medicolegal Institute in London and it will be interesting to see whether, perhaps with its sister societies, it will achieve this ambition before many more anniversaries pass.

5. Pallin, I. M. *Anesthesiology*, 1951, **12**, 583.
6. Phillips, O. C., Frazier, T. M., Graff, T. D., deKornfeld, T. J. *J. Amer. med. Ass.* 1960, **174**, 2015.
7. See *Lancet*, 1956, i, 146.
8. Hill, E. F., Hunter, A. R. *Brit. J. Anæsth.* 1948. **21**, 24.
9. Report on a Confidential Enquiry into Maternal Deaths in England and Wales 1952–1954. Ministry of Health report no. 97.
10. Report on a Confidential Enquiry into Maternal Deaths in England and Wales 1955–1957. Ministry of Health report no. 103.

DRUG TREATMENT OF ASTHMA

WHEN anti-histamine drugs were introduced into clinical practice in 1942 they were expected to prove of value in the treatment of asthma. It was known that in anaphylactic shock in animals histamine was released from the lungs in sufficient quantities to account for the bronchospasm which occurred, and this situation was regarded as an experimental model of human asthma. When specific anti-histamine compounds were found to be effective against anaphylactic shock in guineapigs, hopes were high.

With the delay caused by the war in starting large-scale manufacture of the drugs, and the usual initial burst of optimistic reports, it was several years before they were fully evaluated. Against asthma in man the role of anti-histamines has proved disappointingly small. They are useful in the treatment of infantile asthma, and sometimes in the control of mild asthma clearly due to allergy. In severe and chronic asthma anti-histamines are of little value except as sedatives which do not cause respiratory depression, and as adjuncts to symptomatic remedies and steroids. In consequence, the evidence for the part played by histamine in both anaphylactic bronchospasm and human asthma has been reassessed.

In man, although histamine is released from human bronchi by the allergen, the associated bronchospasm is reduced only by very large doses of anti-histamine drugs.[1] The anaphylactic spasm of smooth-muscle tissues from strongly sensitised guineapigs is equally resistant.[2–4] The doses of anti-histamine required are in fact so large that the compounds themselves cause bronchospasm as a side-effect.[5]

Thus, while histamine cannot be absolved as a causal agent, apparently an additional factor must operate to produce either asthmatic or experimental anaphylactic bronchospasm. Neurogenic mechanisms, acetylcholine, 5-hydroxytryptamine, and a "slow-reacting" substance have all been suggested as culprits. The last substance—SRS-A, a bronchoconstrictor agent of largely unknown nature—has been shown to be released from isolated human asthmatic lung by allergens.[6] Should one or another of these agents be proved to be partly responsible for the bronchospasm of asthma, then a combination of an appropriate antagonist with an anti-histamine drug would probably be of therapeutic value.

It is thus of considerable interest that Kimura et al.[7] have now produced a drug, named homochlorcyclizine, which is not only an anti-histamine but has potent anti-acetylcholine, anti-5-hydroxytryptamine, and anti-SRS-A actions, is a mild sedative—and is a bronchodilator into the bargain. Anti-histamine drugs of the ethylenediamine series in general contain two nitrogen atoms, to one of which aromatic rings are attached, while to the other

1. Schild, H. O., Hawkins, D. F., Mongar, J. L., Herxheimer, H. *Lancet*, 1951, ii, 376.
2. Castillo, J. C. *J. Pharmacol.* 1948, **94**, 412.
3. Green, A. F. *Brit. J. Pharmacol.* 1953, **8**, 171.
4. Hawkins, D. F., Rosa, L. M. Histamine: Ciba Foundation Symposium; p. 180. London 1956.
5. Hawkins, D. F. *Brit. J. Pharmacol*, 1955, **10**, 230.
6. Brocklehurst, W. E. Histamine: Ciba Foundation Symposium; p. 175. London. 1956.
7. Kimura, E. T., Young, P. R., Richards, R. K. *J. Allergy*, 1960, **31**, 237.

aliphatic groups are attached. Homochlorcyclizine was developed following an observation that anti-histamines of this type are least prone to bring about broncho-constrictor effects in large doses if the "aliphatic" nitrogen is incorporated in a heterocyclic ring. In homochlorcyclizine, which chemically is N-p-chloro-benzhydryl-N′-methyl-homopiperazine dihydrochloride, both the nitrogen atoms are incorporated in a heterocyclic (homopiperazine) ring.

The new drug has been tested clinically by Fisherman et al.[8] The results are described as excellent or good in 75% of the 149 asthmatics treated. Even allowing for initial enthusiasm, this suggests a considerable advance on the results with previous anti-histamine drugs. There remains the problem of the 25% of asthmatics who obtain little or no benefit from homochlorcyclizine. In such cases infective agents or structural damage to the lungs may be critically important. On the other hand, the antagonism of SRS-A by the new compound is described as "partial". The concentration of homochlorcyclizine required to antagonise SRS-A seem to be of the same order as that required to antagonise the action of barium on smooth muscle, and its action could therefore be non-specific. Possibly a specific and potent anti-SRS-A effect is essential in a drug that is to be effective against otherwise resistant asthma.

INFECTED COCONUT

THE first hint that a small outbreak of typhoid fever in a suburb of Melbourne might be something out of the ordinary came from the observation that many close contacts of the patients harboured, with or without symptoms, salmonellas other than *S. typhi*. This, together with the wide distribution of the cases, suggested that the epidemic arose, not from a single carrier, but from some foodstuff with a rich and varied flora. The usual vehicles—water, milk, and oysters—were exonerated; but in the course of a systematic investigation of the patients' dietary the health inspector sampled several packets of desiccated coconut from Papua, which were found to contain *S. typhi* and a dozen other species of salmonella.[9] This happened in 1953, and since then the story has been confirmed several times.

In London 9% of 851 samples of desiccated coconut from Ceylon (the chief source of supply to Great Britain) were found to contain salmonellas, and of these the commonest was *S. paratyphi B*.[10] There are good reasons for believing that at least one epidemic of paratyphoid fever in this country was due to this cause.[11] *S. typhi* has, so far as we know, been found in coconut in Australia only. Little effort appears to have been made to warn the public of what is clearly a real, if minor, danger.

Desiccated coconut is usually prepared near the plantation. The nut is shelled and skinned by hand, broken, washed, ground, and dried in an oven at about 200°F. It reaches the housewife without further treatment. It is obvious from several published descriptions that throughout its manufacture it is exposed almost continuously to risks of contamination: from the hands of the workers; from the well water in which it is washed; and from the birds and animals great and small which stray about the factory. To define the main sources of the salmonellas calls for extensive work on the spot, and until this is done no rational method of preventing infection can be devised. The coconut clearly never reaches the temperature of the oven in which it is dried, and experiments have shown that a higher temperature makes it unacceptably brown.[12]

One result of these investigations has been that port medical officers now sample desiccated coconut on arrival from abroad, and Professor Semple and his colleagues[13] in Liverpool have drawn attention to some of the problems involved. They have isolated 34 species of salmonella, but some of these have never been known to cause disease in man. If the presence of any one of these was taken as ground for condemning the whole consignment, the trade would probably end at once. The Liverpool authorities have taken a bold and (we think) sensible decision. Experience in this country teaches us that *S. paratyphi B*, *S. thompson*, and *S. typhimurium* are frequent causes of serious disease, and these three species have been designated as menaces to the public health. The dangers arising from the other species are of a different and lesser order. 5% of the bags in every consignment are examined for salmonellas. If no "designated salmonellas" are found the consignment is released. If "designated salmonellas" are found a further 10% sample is examined. If more "designated salmonellas" are found in this 10% the whole consignment is condemned: if they are not, only those bags which have been found to be infected are destroyed. The purist may say that Semple should allow no food containing potentially pathogenic organisms to reach the public; or he could be criticised for not having designated a larger number of species. In 1959 *S. newport* caused 319 notified cases of food-poisoning in England and Wales, *S. infantis* 57, *S. bareilly* 26, and *S. seftenberg* 13[14]; and all these have been isolated from coconut in Liverpool. (Whether the exotic species of salmonella found so far only in protein wastes and the bowels of reptiles are pathogenic to man we can know only by experience.) Boycott et al.[15] suggested that the salmonellas commonly pathogenic to man are common because they are more pathogenic than the others, and, if this is so, Semple's decision seems justified.

WORK IN PREGNANCY

THE early weeks of pregnancy must be a little like the first few weeks of a new job: everything is different; the new is not always welcome; even the job itself may be unwanted. Often the mother will accept the new task of having a baby with joy, putting it before all other claims on her time; but occasionally she carries on as if nothing much had happened—even to the extent of continuing in heavy work, as Professor Russell and Miss Walton remark in a letter on p. 668. Though it is difficult, if not impossible, to prove that such activity is harmful, most obstetricians would say that it was. The special care of the pregnant woman under our excellent maternity services is concentrated on the final six months; and the time may be ripe for some shift of emphasis towards the earliest months. In the United Kingdom each year, possibly a quarter of a million pregnancies go wrong in one way or another in the first three months.

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Needs and Beds

PULLING DOWN THE OLD MENTAL HOSPITAL

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OUR mental hospitals are big because they accommodate so many long-stay patients, who fill about three-quarters of the beds. Some people think that with modern therapeutic advances, rehabilitation, and improved social services, a time will come when there will be no long-stay patients. Others believe that the demand for long-stay beds will be as great as ever, or may even grow because of the longer span of life. Since nearly half the beds in this country are occupied by psychiatric patients, the way they are used in the future will affect the hospital policy of the whole country. If they become empty, we must consider whether they should be filled with other patients, whether the hospital should be converted to another use, or whether it should be closed. In this paper I set out some facts and some opinions in the hope of stimulating further discussion.

SOME FACTS

In 1958 we made a census of all the patients at Banstead Hospital. These were 828 men and 1271 women. Of these, 283 men and 750 women were over the age of sixty. There were thus three times as many elderly women as men, and this discrepancy accounts entirely for the disproportion of women to men in the hospital. More than half the patients had been admitted before 1950 and about 40% had been in the hospital since before 1940.

To ascertain what type of patient is likely to form the long-stay population of the future, the 1957 admissions still in the hospital at our 1958 census were reassessed in 1960. Of the original group of 574 men and 820 women admitted in 1957, 69 men and 62 women remained in hospital on July 31, 1958. Between then and July 31, 1960, their number diminished as follows:

	Men	*Women*
Discharged to community	15	13
Died	4	22
Transferred to other hospitals	1	2
Patients with tuberculosis awaiting transfer to original hospital	29	0

This left 20 men and 25 women still in the hospital. Their status is shown in the accompanying table.

The most striking observation was the high death-rate among the women. Of the women still in hospital, nearly half were senile, with an average age of eighty-one. The death-rate among the men had been much lower; the average age of the 2 senile sick was sixty-eight.

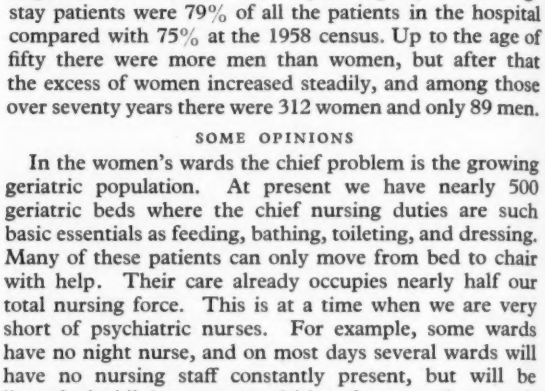
CLINICAL STATUS OF LONG-STAY RESIDUE

—	Men	Women
Senile sick	2 (av. age 68 years)	11 (av. age 81 years)
Schizophrenia	9	4
Organic nervous illness	3	6
Likely to leave hospital soon	2	3
Could leave but refused	2 (43 years)	– (61 years)
Recurrent mania	–	1
Chronic alcoholism	1	–
Schizophrenia and tuberculosis	1	–

A fresh census of all inpatients was made in July, 1960. Since 1958 the total number of patients in the hospital had dropped from 2099 (828 men and 1271 women) to 1847 (790 men and 1057 women), a fall of 12%. (There had been a reduction of about 100 patients a year over the last five years.) The number of patients who had spent more than nineteen months in hospital was 1460 compared with 1578 two years before. Again there was a large number of women over sixty (see figure). These long-stay patients were 79% of all the patients in the hospital compared with 75% at the 1958 census. Up to the age of fifty there were more men than women, but after that the excess of women increased steadily, and among those over seventy years there were 312 women and only 89 men.

SOME OPINIONS

In the women's wards the chief problem is the growing geriatric population. At present we have nearly 500 geriatric beds where the chief nursing duties are such basic essentials as feeding, bathing, toileting, and dressing. Many of these patients can only move from bed to chair with help. Their care already occupies nearly half our total nursing force. This is at a time when we are very short of psychiatric nurses. For example, some wards have no night nurse, and on most days several wards will have no nursing staff constantly present, but will be "overlooked" by a nurse visiting from another ward. Much of the psychiatric training given to our nurses is



Long-stay population (admitted in 1958 or earlier) distributed by age and sex.

thus wasted, and any student nurse entering the hospital will see for herself that once she is trained she is likely to spend half her time as a geriatric rather than a psychiatric nurse. On the male side this problem is much less acute.

On the present expectation of life, in twenty years' time about 300 men and 300 women from our present long-stay population should still be alive and could still be in the hospital. Many of these, however, should have been able to return to the community. We have already rehabilitated apparently incurable patients without the help which the local authorities may be expected to provide under the new Mental Health Act. If even 5% of these patients were discharged yearly, in twenty years' time none would be left.

We must, however, consider whether we are not building up a new long-stay population from our present admissions. On the evidence this seems unlikely. It is not unreasonable to assume that the 13 schizophrenic patients remaining from our 1957 admissions could be rehabilitated, and the total numbers are very small—i.e., 45 now remaining out of a total admission of 1394 from a catchment area of nearly three-quarters of a million

people. If adequate provision is made for the elderly, there should be only a very small residue—mostly patients with neurological diseases.

At present the mental-hospital system is developing by trial and error. Psychiatrists and psychiatric nurses are leaving the mental hospital to work in the community, and health visitors and other community workers are coming more freely into the mental hospital. We must recognise, however, that there is much anxiety due to uncertainty about the future. Psychiatric nurses may be diffident about training in a mental hospital because of the number of senile patients. The changing character of the hospital adds to this anxiety. Rumours that some hospitals will become a " dumping-ground " for the chronic patients of more active units or for geriatric patients from large cities are discouraging. As new units appear in the community, they will undoubtedly attract both nurses and psychiatrists from our present hospitals. If, at a time when fewer patients with a good prognosis are being admitted to the mental hospital, many of the staff leave to work elsewhere, deterioration within the mental hospital will be unavoidable.

Treatment in the mental hospital depends on the attitudes, the expectations, and the morale of those who work in it. Successful rehabilitation needs an atmosphere of therapeutic optimism. We have shown that an active therapeutic regime produces worthwhile results among admissions and long-stay patients alike, and steadily reduces the total number of patients in the hospital. A change in attitude or a fall in morale, however produced, could readily refill these same empty beds.

But if our present policies continue and the community provides help in resettlement, I think that the hospital will continue to empty. Morale can be maintained if nurses and doctors are able to work not only in the mental hospital but also in the new units which will appear. Just as some hospitals are developing a general-practitioner service for patients who only need general-practitioner care, so there would seem to be a good case for developing a general nursing service to care for those patients, particularly geriatric, for whom specialised psychiatric care is no longer appropriate.

It would, of course, be possible to fill the empty beds at this or other mental hospitals with other patients—geriatric, subnormal, or others. But whichever type of patient is sent, nothing will alter the serious defects of many of these institutions. Fundamentally they increase the patient's isolation, and by their very size frustrate the formation of therapeutic communities. It could be argued that if we must have short-stay and long-stay units which are separate from each other, the short-stay unit should be in the present mental hospital, because short-stay patients can usually overcome this handicap. On the other hand, the long-stay unit should be in the community, for its patients are in greatest need of a situation where transition from hospital to community life is easy. The long-stay patient leaving his ward to go to sheltered work should rub shoulders with potential landladies and potential workmates and not, as at present, merely with other patients.

I have written this paper from experience at one hospital, and perhaps it does not apply to others. Nevertheless, discussion with colleagues suggests that many mental hospitals are now reducing the number of their beds, and share the problems of physical conditions and emotional attitudes which beset us here. It would seem essential that developments should be freely discussed if we are to plan for the material needs of the future psychiatric services and relieve the anxieties of the present psychiatric staff. We see slums pulled down and new houses built; new roads replace the old. Only when the old mental hospitals are pulled down will there be the opportunity to provide a new service in keeping with present needs.

Special Articles

MEDICAL STAFFING OF HOSPITALS

THE Joint Working Party on the Medical Staffing Structure in the Hospital Service, set up in 1958 under the chairmanship of Sir Robert Platt, P.R.C.P., has now reported.[1] The working party was appointed by the Minister of Health and the Secretary of State for Scotland in collaboration with the Joint Consultants Committee, the Royal Scottish Corporations, and the Central Consultants and Specialists Committee.

The main feature of the report is a recommendation that the staffing structure should include a new grade below that of consultant. Those in this grade, to be known as medical assistants, would normally have held a registrar post for at least two years. Appointment would not be of limited duration; and remuneration would be on a long incremental scale, extending high enough to make this a career grade. Other features of the report are its insistence on the need to make better use of consultants' time and for their closer integration through the " firm " system, and on the need for help from general practitioners in the hospital system. The number of consultants is found to be still insufficient.

DEVELOPMENT OF EXISTING STRUCTURE

The working party recalls that the Spens Committee on the Remuneration of Consultants and Specialists, which reported in 1948, seems to have taken the view that in general the doctors between house-officers and consultants would be aspiring to consultant posts, and that these doctors should, throughout their service in these intermediate grades, concentrate as trainees on one particular specialty. But, after discussions on the committee's report between the Health Departments and representatives of the profession, the grades of senior and junior hospital medical officer (both of unrestricted tenure) were added. A few years ago it was agreed that, pending the outcome of the working party's study, hospitals with large casualty departments might be authorised to appoint a senior casualty officer for a term of four years on a salary scale within that applicable to senior hospital medical officers.

In 1950 junior registrarship ceased to be treated as essentially a training grade for the post of consultant or senior hospital medical officer; and the name of this grade was changed to senior house-officer. The next year the registrar grade ceased to be looked on as primarily a training grade. In practice senior-house-officer and registrar appointments have commonly been held for longer than the one year and two years, respectively, named in the Terms and Conditions of Service. "We have been told," says the working party, " that most regional hospital boards keep good registrars as long as they wish to stay." The posts are not necessarily graded according to the nature of the work: " Where difficulty is experienced in filling a house officer post it is not uncommon for it to be transferred to the senior house officer grade in the hope that the higher salary will attract applicants."

In 1951 the normal tenure of a senior-registrar post was extended from three to four years; and at present even this longer limitation on tenure is in abeyance.

1. Ministry of Health, Department of Health for Scotland. Medical Staffing Structure in the Hospital Service: Report of the Joint Working Party. H.M. Stationery Office. Pp. 89. 5s.

GENERAL CONSIDERATIONS

The excess of senior registrars, though now smaller, persists.

"At the same time contentions have been common that by reason of inadequacies in consultant staffing members of grades below the consultant grade are undertaking consultant work and responsibility. Concurrently many non-teaching hospitals have been unable to attract sufficient doctors to build up adequate staffs of house officers and registrars.

"In the evidence submitted to us there is a noteworthy absence of testimony that the present structure has proved satisfactory in all respects, or is the best that can be devised. On the contrary some criticism of it is expressed or implied in all the general evidence received, though there is no unanimity on its shortcomings or on how they should be remedied."

A basic question raised by the different criticisms is whether a staffing structure designed for training in a specialty can effectively fulfil service needs.

GENERAL PRINCIPLES

The structure must be based on consultants, who are recognised as qualified to take full personal responsibility for the complete medical care of all patients in their specialties. The structure must further provide for: (1) doctors required to assist consultants in the day-to-day care of their patients; and (2) doctors needing postgraduate experience and training. Whatever these assistants do for patients "must be done, and be openly recognised as being done, on behalf of and under the direction of the consultant".

Advancement from one grade to another should be competitive; and some doctors who aspire to higher appointments will fail in the competition.

"On occasion these doctors may have become so specialised that this fact and their age become an obstacle to their obtaining suitable work in their profession outside the Hospital Service. By that time their experience and skills are, however, bound to be of such value to the Service that the structure should provide ways and means by which such doctors may be retained in it and on a permanent basis where appropriate."

The hospital structure should provide suitable places for: (*a*) new graduates who need the hospital experience which is a prerequisite to full registration; (*b*) doctors who wish to obtain further postgraduate experience, whether or not they will be making their careers in the hospital service; and (*c*) suitably qualified doctors in other branches, especially general practice, to engage in hospital work for part of their time.

CONSULTANTS

In the ten years 1950–59 the number of consultants increased by 37%—from 5610 to 7680. But, as the average amount of time for which a part-time consultant is employed has increased, the amount of consultant service increased by more than 37%.

Excessive Delegation of Duties

Evidence received by the working party indicates that work properly belonging to consultants is being regularly discharged by senior registrars and others; and it suggests that the number of consultants is still inadequate. The working party is satisfied that, of the several possible reasons for this state, resistance by the Minister to proposals for new appointments is not one.

Ensuring that consultant work is done by consultants is not only a matter of numbers: it is a matter of organisation. Some consultant appointments entail a disproportionate amount of travelling between hospitals—which is tantamount to consultant time wasted. "We have also met cases in which the consultants live so far from the hospitals in which they are responsible for patients as to make impossible their personal attendance in emergency."

General Principles

The working party lays down the following general principles:

1. All patients in the hospital service should be in the charge of consultants.

2. A consultant's obligations are not restricted to certain fixed sessions: he has an inescapable continuing responsibility for his patients (inpatients and outpatients alike) at all times.

3. Doctors below consultant rank should act as assistants to the consultants.

4. The time that a consultant devotes to any given hospital should suffice to enable him to discharge his responsibilities. "In hospitals largely concerned with the treatment of acute illness, the aim should be for every inpatient to be seen by the responsible consultant at least two or three times a week. Outpatient arrangements should be such that junior staff are not left in sole charge, except in the occasional unavoidable absence of the consultant."

5. Where practicable, small part-time appointments should be absorbed into the duties of existing staff or, failing that, should be grouped together to form appointments for a worthwhile amount of time.

6. The work of a consultant should be confined to as few hospitals as circumstances will permit. In any event he should have a main attachment to one hospital or hospital centre, and he should live within easy reach of this.

7. The duties required of each consultant should be defined precisely in his contract.

Organisation of Consultant Service

Where two or more consultants in the same specialty are employed in a single hospital there is everything to be said for bringing them into a relationship which will (*a*) facilitate continuous and effective consultant cover for all patients, and (*b*) have some regard, in the distribution of work, to the factor of seniority in the consultant grade so that the younger consultants do more of the physically more strenuous work. Under this "firm" system, the younger consultant carries the same clinical responsibilities, and has the same clinical independence, as his senior. The system can also be instituted where two consultants are individually associated with different hospitals, provided these are reasonably close to each other.

Where there is need for more consultant service but there is not scope for another consultant with responsibility for a substantial proportion of the beds, the need may be met through a variant of the "firm" system.

In such a case the necessary relief might be provided by associating with the existing consultant or consultants another doctor of consultant rank, who would be appointed as a consultant on condition that he worked for the time being in supplementing the work of the consultants with whom he is associated. "In essence he would become the junior partner of a firm." He should always be given some beds as of right; and when a consultant vacancy arose in the hospitals in which he was serving he would be given a full number of beds and a normal range of consultant duties.

SENIOR REGISTRARS

In some specialties (for example, mental health, radiology, and anæsthetics) the number of senior registrars is less than the number of training posts; but in other specialties the number of senior registrars greatly exceeds the number of training posts.

Undertaking the work of consultants is a vital part of the training process. What is wrong is that senior regis-

trars, or others, should be expected or permitted to undertake consultant responsibility as a matter of routine.

"Temporary delegation of consultant duties is permissible only when there is available a consultant to whom the doctor performing the delegated duties can turn for advice, e.g., when a consultant is on leave there must be another consultant available to whom reference can be made."

The working party denies that there is a special class of work which may be called "senior registrar" work. This is a training, and not a service, grade.

"We find no need to suggest any change in the work and responsibility which a senior registrar should properly undertake. Though some consultant work must be undertaken in the latter part of training, such work should be done under consultant supervision and should not be performed independently, as a routine, as is often happening now."

Four years' tenure should not be regarded as a rigid maximum or minimum.

Selection and Review

The working party recommends that the appointments committees for selecting new senior registrars, whether for teaching or for non-teaching hospitals, should include representatives from both classes of hospital. A report should be made on each new senior registrar a year after the start of his appointment, with a view to a firm decision by the time he has been in the grade for eighteen months as to whether he is suitable for retention at the end of his second year.

Rotation between Teaching and Non-teaching Hospitals

Senior registrars trained in teaching hospitals have had an advantage in the competition for consultant posts over those trained in non-teaching hospitals. Accordingly either all senior registrars should be trained in teaching hospitals or all senior registrars should be trained partly in each of the two types of hospitals. The working party favours the latter course as the customary one. The necessary link between the teaching and the non-teaching hospitals may best be maintained through committees established by the regional boards and the boards of governors jointly in England and Wales and by the regional boards in Scotland. Such committees, which should consist entirely of medical members, would supervise training arrangements, receive reports on all senior registrars at the end of their first year of service and advise on whether the appointment should be continued, and advise on what course a senior registrar should take if he has failed to gain a consultant post at the end of his fifth year in the grade.

NEEDS TO BE MET BY DOCTORS OTHER THAN CONSULTANTS AND SENIOR REGISTRARS

The initial tenure of a house-officer, senior house-officer, or registrar should be settled between the employing authority and the doctor at the time when the appointment is made: this should be up to one year for house-officers and senior house-officers and two years for registrars. At least twelve months' continuous service as a fully registered house-officer or a senior house-officer, or its equivalent, should normally be required of a candidate for a registrar appointment.

The working party gathered evidence that the number of graduates in Great Britain is expected to fall from an annual average of 1780 in 1955–60 to an annual average of 1700 in 1961–64. Even now, without the 3628 doctors from overseas, there would be a breakdown of staffing below the senior-registrar grade; and some decline in the number from overseas may follow the development of postgraduate training for such doctors in their own country.

Because of the existing shortage in these junior grades, those in them—especially those in non-teaching hospitals—are overworked. Moreover, not only the number but the quality of candidates for appointments are not always satisfactory. Notwithstanding uncertainties

"on one point there can be no doubt: the Hospital Service cannot hope to have an adequate and efficient staff of fully registered housemen and registrars unless reasonable prospects of a good career in some branch of medicine can be seen by the doctors who stay in the Service to work in these capacities".

Longer Hospital Service by Young Doctors

Ideally new entrants to general practice should have spent at least two years in the hospital service after becoming fully registered; and greater flexibility in arrangements for tenure of posts in the house-officer and registrar grades may attract prospective general practitioners. The possibilities offered by arrangements under which prospective general practitioners split their time between hospital work and work as trainee assistants in general practice should not be overlooked.

General-practitioner's Role

There is scope for more help to the hospitals from suitably qualified general practitioners as medical assistants who would visit the hospital daily and supervise house-officers, and as clinical assistants at special clinics. In some instances a general practitioner who has continued work in the hospital service might later be chosen for a consultant post, and pursue this career concurrently with one in general practice.

The Need for a New Grade

The number of senior hospital medical officers, absolutely and relatively to the number of consultants, declined between 1953 and 1959. After hearing arguments for and against the retention of the S.H.M.O. grade the working party came to this conclusion:

"Some members of it carry full clinical responsibility . . . If it were to be continued otherwise than as a transitional measure for making provision for those already in it major changes would be required: it is too near to the consultant grade in status to be a satisfactory part of a permanent structure and we cannot therefore recommend its continuance as a permanent feature."

This grade should be closed to new appointments.

A new grade of unlimited tenure not above senior-registrar level is required for the senior registrar who, having completed his training, does not proceed to a consultant appointment; for some registrars to enable them to remain in the hospital service in a position of security; and for some general practitioners. These new posts should be a supplement, not an alternative, to measures to encourage young doctors as a general rule to stay longer in hospital work after the year of provisional registration, and to provide wider opportunities for general practitioners to assist in hospital work.

Admission to the new grade should normally be restricted to doctors who have held a registrar appointment for at least two years and have worked in the hospital service for at least three years since full registration. Appointment should not be of limited duration. The work common to all specialties in which the members of this grade might properly engage is work such as is done by registrars. All members of this grade should work as assistants to consultants and under their supervision, except any in ophthalmology who may be engaged solely on refraction.

The generic name of the grade should be medical assistant, but in the specialties (other than general medicine in which "medical assistant" is appropriate also as a specific name) the appointments should be known as assistant in surgery, assistant in chest medicine, &c. Members of the grade should be recognised as potential candidates for consultant appointments.

The suggested grade would consist of doctors with widely varying experience; and accordingly a long incremental salary-scale seems to be indicated. Time-expired senior registrars might enter the scale at a point that took account of the salary they had received as senior registrars. "For recruitment the scale must hold the promise of an ultimate reward sufficiently high to make the grade a career grade for those doctors who have to spend the remainder of their professional life in it and to attract into it suitably qualified general practitioners for part-time work."

REVIEW AND REORGANISATION

The working party recommends that regional boards and boards of governors should institute a review in the light of the working party's report, and should report to the Minister proposals for (*a*) additional consultant appointments regarded as necessary immediately, and (*b*) posts in the medical assistant grade. In framing their proposals the boards should examine carefully the possibilities of adopting the "firm" system more widely, and of reducing time lost by consultants in travelling and in other unprofitable ways.

The working party suggests that the Minister should seek advice on the proposals for additional consultant appointments and for the establishment of medical-assistant posts from a professional committee consisting of members appointed by him and by the Joint Consultants Committee.

After the introduction of the new grade, no further junior hospital medical officers or senior casualty-officers should be appointed.

THE "ARTIFICIAL MUSCLE" OF McKIBBEN

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THE McKibben muscle, more commonly known as the "artificial muscle", is used in the U.S.A. to help provide some active movement for patients with severe flaccid paralysis of the upper limbs. This device was invented by Mr. J. L. McKibben, a Los Angeles physicist; and its use has been developed by Dr. Vernon L. Nickel and his team at Rancho Los Amigos Hospital, near Los Angeles.

The "muscle" consists of an inner rubber tube contained in an outer cover of double helical nylon weave. Inflation of the tube causes the "muscle" to shorten, and in so doing it develops a substantial mechanical pull. The strength of pull is varied by the amount of inflation. The "muscle" in fig. 1 is 7 in. long. It is seen at rest and lifting a 7 lb. weight through $1^{3}/_{4}$ in.

Carbon dioxide gas is used to inflate the "muscle". Its flow is controlled either by a system of mechanical valves or, for patients with very slight residual power, by an electrical system in which microswitches activate D.C. gas solenoids. Both systems offer three positions—"operate", "release", and "hold". The "hold" position enables a contraction to be maintained without further voluntary effort, and without further consumption of carbon dioxide.

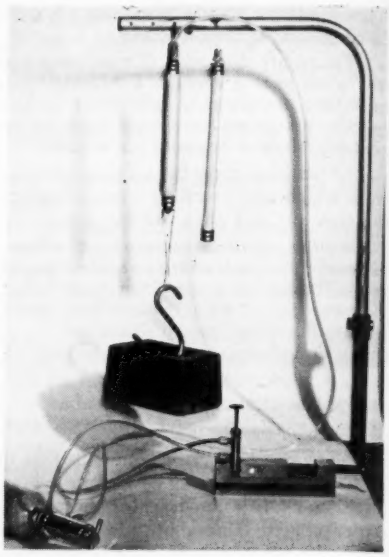


Fig. 1—The McKibben "artificial muscle": shortened by inflation and lifting a 7 lb. weight; and at rest.

A gas cylinder, 7 in. long and weighing about $17^{1}/_{4}$ oz. when full, usually lasts one "muscle" for 4–5 days, and two "muscles" for half that period. It can be attached to bed or wheelchair, or carried in the pocket. Patients can have a cylinder-recharging equipment for use in their own homes. The "muscle" is remarkably durable and usually lasts for many months: it is easy and cheap to replace.

The commonest uses of the "artificial muscle" so far have been to work a flexor hinged splint so as to give a "pinch" between the thumb and the first two fingers (fig. 2), and to help move a ball-bearing functional arm support to give flexion and extension of the elbow. Other uses of its muscle-like properties can be devised according to individual needs—e.g., to move a tray from side to side to bring different objects within a limited reach. Several "muscles" can be fitted to one patient to give different movements, provided sufficient residual power can be found to work them. A patient can sometimes control three or four separate "muscles" with one foot.

The use of the "artificial muscle" and the associated splints, feeders, &c., requires not only a basic knowledge of the management of paralysed limbs, but also technical training in designing, making, and fitting these special devices to the individual limb, and in the education of the patient in their use. One of us (A. L.) has attended an intensive course at Rancho Los Amigos Hospital, and work on these lines is now proceeding at Mary Marlborough Lodge—the Disabled Living Research Unit which has been built in the grounds of this hospital with

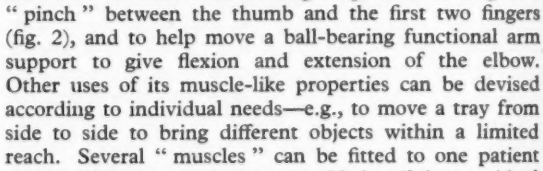


Fig. 2—The "artificial muscle" acting on a rancho hinged flexor splint to give an effective "pinch".

funds provided by the National Fund for Research into Poliomyelitis and Other Crippling Diseases. Similar work can be seen in Scotland at the Princess Margaret Rose Hospital in Edinburgh (Mr. D. W. Lamb).

Arrangements for the supply in this country of rocker feeders, suitable gas cylinders, valves, and the necessary ancillary equipment are nearly complete, and we shall be glad to hear from other workers who are interested and might like to take advantage of these arrangements.

It is a pleasure to pay tribute to Dr. Nickel and his team, who have not only put to such good use Mr. McKibben's original ingenious invention, but have devised the whole range of 'Rancho' splints, rockers, and operative techniques which make their centre outstanding in this field. Particularly we should like to acknowledge the generosity with which they give so much time to sharing their knowledge with the many visitors from this country who visit Rancho to learn about their work.

Our special thanks are due to Prof. J. Trueta, whose support has made A. L.'s visit to the U.S.A. and the subsequent work possible; the National Polio Fund financed the project at his request.

The Wider World

NEW HOSPITAL IN ARABIA

A FEW miles south of Kuwait, on the Persian Gulf, is one of the world's great oilfields, worked by an Anglo-American company. The oil town of Ahmadi, built in unpromising desert, looks at first sight like a London suburb, with its treelined roads and bungalows; but, like Kuwait itself, it depends largely on water distilled from the sea by means of the gas which comes up with the oil. The town and oilfield together have a population of some 15,000, of whom about 2100 are British and 100 American, while the others mostly come from one of the Arab countries, from Iran or from Pakistan.

The first hospital of the Kuwait Oil Company was a small one established in Kuwait town in 1947; but in the following year it was moved to Magwa, near Ahmadi and the oilfield, where the local needs led to its steady development. Additions included an isolation block, a family annexe, and a maternity unit; and after ten years admissions numbered about 350 a month, with nearly 19,000 outpatient attendances.

Last April this Magwa hospital was replaced by a completely new one in Ahmadi. A great deal of thought has been given to the design of this modern hospital for a very hot country, and some of the decisions will be of interest to others concerned with building hospitals or working in them.

To protect the hospital from the sun by orientating the buildings south/north proved to be incompatible with medical needs. Instead, therefore, wide verandahs and balconies were incorporated in the two-storey ward blocks, and the single-storey buildings were given sun-baffles. The buildings have been arranged to afford the greatest possible shelter from the prevailing northwest wind, which occasionally brings sand-storms.

Constructed on a light steel-lattice framework, the buildings have concrete floors and aluminium roofs. The external walls are of brick or rendered concrete blocks, with fly-screened doors and windows. Internal partitions are also made of concrete blocks, except where movable metal partitions are used to give fluidity in layout. The glass partitions dividing the main wards are also movable. The ceilings are everywhere made of acoustic tiles.

Fig. 1—Outside a two-storey ward block.

An informal appearance is given to the buildings by having a number of small courtyards among them. A careful selection of colours, both within and without, helps to give a cool and restful effect throughout the hospital.

The service areas are so planned that a complete diagnostic service is available at one point; all hospital issues are made from another; and all medical stores received at a third.

The air-conditioning plant is intended to operate all the year round, and is designed so that major overhauls can be carried out without disturbing the medical functions of any of the buildings. In an emergency, all ventilating fans are switched off by automatic fire-detectors.

In each ward, piped oxygen is taken to a few beds which are also connected to a suction line. A vacuum system for floor-cleaning is ducted into the walls, and dirty linen and all ward refuse are disposed of through chutes leading to closed containers outside the hospital.

Hospital messengers are not required, since all wards and departments are connected by a pneumatic-tube message system whose cylinders take documents and small packages.

The wards are on two floors because the greater compactness promotes efficiency of nursing as well as comfort for the patients. The hospital has 200 beds, distributed among eight wards, and a typical ward has 40 beds in two groups of 20. In

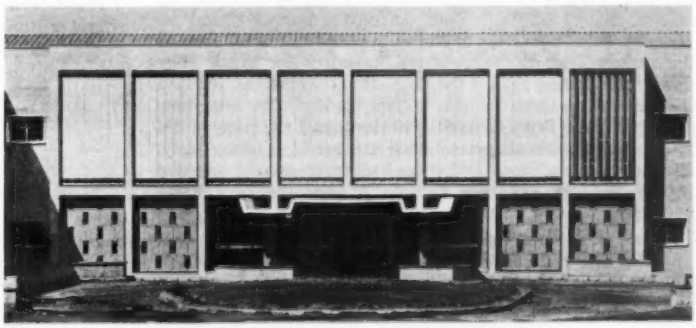


Fig. 2—Main entrance to the Southwell Hospital.

each group of 20, 16 beds are arranged in 4-bed bays, while 4 are in single rooms. The 20-bed units are arranged in the shape of an L, with the ward-sister's station in the angle. Nearest the sister's station are the single rooms, the utility and treatment rooms, and the patients' dayrooms. Thus the sister is placed centrally in her nursing unit.

The groups of 4 beds are meant to give some privacy but also some companionship. All wards, except isolation, have dayrooms to encourage patients to be ambulant as soon as possible. The dayrooms open on balconies or verandahs, and overlook an inner courtyard.

The surgical suite—near the surgical wards, central sterilising unit, and X-ray unit—has two theatres, linked by an autoclave and sterilising room. Anæsthetic gases are piped to the anæsthetic rooms and theatres. A separate air-conditioning plant serves the theatres.

There is a well-equipped physiotherapy unit with a small gymnasium. A special room is set aside for occupational therapy, which is also carried out in the wards.

In the outpatient department, care has been taken to get rid of the grimness of most hospital waiting-rooms. Seats are arranged in informal groups, and bright colours are freely used.

All articles for wards, outpatients, and surgical theatres are sterilised in a central unit. The only instruments sterilised in the theatre unit are those for major surgery. No sterilising is done in the wards or outpatient department.

Fig. 3—General view of a ward.

The medical staff consists of a chief medical officer, a hospital superintendent, six specialist, and general medical officers.

Called the Southwell Hospital after Sir Philip Southwell, this building was completed in twenty-one months. The architects and consulting engineers were Messrs. Huckle & Durkin of London and Liverpool, and construction was by the Contracting and Trading Company.

Medicine and the Law

The Eternal Swab

A WIFE, after an operation on Jan. 24, 1955, to assist conception, conceived a child, but on Feb. 1, 1956, when she was three-and-a-half months' pregnant, she had a severe internal hæmorrhage due to a " ruptured ectopic pregnancy ".

She was taken to the Nairobi European Hospital, where she arrived almost dead, pulseless, and grey-blue in colour, and was operated on. Two or three months later she had severe internal pains, and after admission to the European Hospital again she was operated on by a surgeon who found much of the bowel inflamed and had to cut away 7 ft. of it. Inside that length of bowel there was found a piece of towelling material 9-10 in. long and 7-8 in. wide. On June 29, 1957, the wife and her husband sued the first surgeon and the hospital authorities for negligence. The trial judge found against both defendants and awarded special damages to the husband and wife, amounting to Shs. 5189, and also general damages to the wife, amounting to Shs. 50,000 (£2500). Both defendants appealed, and on Nov. 24, 1958, the Court of Appeal for Eastern Africa allowed the surgeon's appeal and entered judgment for him. They upheld the finding against the hospital authorities but reduced the general damages to Shs. 15,000 (£750). The wife now appealed to the Privy Council. On the appeal the surgeon did not dispute that an abdominal pack had been left in her body, and the question was whether he had failed to take any due precaution or to use due care to prevent the pack being overlooked.

Lord DENNING, giving their Lordships' judgment allowing the appeal, said that once it was held that a swab *was* left in the body there must have been some mistake made both by the surgeon and the hospital authorities.

So far as the surgeon was concerned there must have been a swab left by him or his assistant, either a restraining or a mopping swab. So far as the hospital authorities were concerned, there must have been a mistake either on the check-in or the check-out of the swabs. Although there must have been some mistake, it did not follow there was negligence. The whole team were engaged in a race against time. They were under extreme stress. A mistake which would amount to negligence in a " cold " operation might be no more than a misadventure in a " hot " one. But the difficulty was that there was no evidence to suggest what kind of mistake that would be. The trial judge found the surgeon to be negligent in leaving a swab, and the hospital authorities negligent in making a wrong count. The Court of Appeal, while upholding the finding against the hospital authorities, reached a different conclusion with regard to the surgeon. " The only probable source of error disclosed in the evidence," said Briggs, V.-P., " is that one of the bundles (on the incoming count) contained not three, but four packs . . . It appears to me that two old and thin packs, with the tape of one between them, might easily feel and look like one fairly new and thick one and might be miscounted in haste . . ."

While their Lordships fully appreciated the reluctance of any tribunal to arrive at a finding of negligence against a highly skilled surgeon who had successfully performed a most difficult operation, they felt bound to say that it was not open to the Court of Appeal to speculate in this way without any evidence to support it. The possibility of two packs being stuck together was never suggested as an explanation by anyone.

Their Lordships found that the trial judge was justified in his finding that if the pack was a mopping pack, it was negligence on the part of the person who used it, whether it was the surgeon or his assistant, to lose control of it and leave it in the body. If it was a restraining pack, having regard to the small number used and their obvious position, the absence of movement and the lack of any particu-

lar need for haste at the conclusion of the operation, it was negligence on the part of the surgeon not to remove it, the responsibility being, as he admitted, on him to do so, and there being no justification for the departure from the normal routine. Their Lordships were of opinion that the Court of Appeal ought not to have reversed the trial judge on this point. As to damages, the trial judge might have erred on the high side, but not so much as to make it wholly erroneous; this was not a case where the Court of Appeal should have interfered with the assessment of the trial judge, whose judgment would be restored.

Cooper *v.* Nevill and Another—*Judicial Committee of the Privy Council:* Lord Tucker, Lord Denning, and Lord Morris of Borth-y-Gest: March 9, 1961. Counsel and Solicitors: James Stirling, Q.C., and Adrian Head (Merriman, White & Co.); John Thompson, Q.C., and Frederick Hallis (Lovell, White & King).

CHARLES CLAYTON
Barrister-at-Law.

Use of the word "Insanity"

THE appellant was convicted on May 14, 1960, in the Supreme Court of the Bahama Islands before Henderson C.J. and a jury of the murder by stabbing on Feb. 17, 1960, of an overseer at the Fox Hill prison, when the appellant, who was a prisoner there, was attempting to obtain keys with a view to escaping. He had been sentenced to death. He now appealed to the Privy Council *in forma pauperis* by special leave. At his trial he had raised the defence of diminished responsibility under s.2 of the Homicide (Special Defences) Act 1959 of the Bahama Islands (identical with s.2 of the English Homicide Act 1957). The ground of his appeal to the Privy Council was that the judge had wrongly directed the jury on that issue.

Lord TUCKER, giving the judgment, said that the Chief Justice, in directing the jury on the issue of diminished responsibility, quoted in full the rule in McNaughten's case and observed "it is not this case, but I want you to see what insanity is so that you can see whether it is borderline or not". Their Lordships were of opinion that the direction given to the jury by which they were told to assess the degree of abnormality of mind in terms of the borderline between legal insanity and legal sanity as laid down in the McNaughten rules was a serious and vital misdirection which would, no doubt, not have been given had the Chief Justice had the benefit of Lord Parker, C.J.'s subsequent judgment.[1] If insanity was to be taken into consideration, as would usually be the case, the word must be used in its broad popular sense. The direction to the jury must always be related to the particular evidence, and the words "borderline" and "insanity" might not in some cases be helpful. There was a further misdirection when the judge said: "Did he intend to do it? If so, murder; if not, manslaughter." A man might know what he was doing and intend to do it and yet suffer from "such abnormality of mind as substantially impaired his mental responsibility" (s.2 of the Homicide Act). That misdirection might have been a determining factor in the jury's verdict. The appellant was deprived of his right to have his defence of diminished responsibility properly considered by the jury, and the verdict of murder and sentence of death must be quashed, and a verdict of manslaughter and a sentence of imprisonment for life substituted therefore.

Rose *v.* The Queen—*Judicial Committee of the Privy Council:* Lord Tucker, Lord Denning, Lord Morris of Borth-y-Gest: March 6, 1961. Counsel and Solicitors: J. T. Malony, Q.C., and D. A. Grant (Blyth, Dutton, Wright & Bennett); Neil Lawson, Q.C., and Mervyn Heald (Charles Russell & Co.).

CHARLES CLAYTON
Barrister-at-Law.

1. Reg. *v.* Byrne (1960) 2 Q.B. 396; see *Lancet*, 1960, ii, 103.

Conferences

CLINICAL ASPECTS OF GENETICS

THE Royal College of Physicians of London held a conference on the Clinical Aspects of Genetics on March 17 and 18. The opening session and the final session were clinically oriented; in between were sessions on the two more scientific branches of genetics which have clinical applications—cytological genetics and biochemical genetics.

Dr. J. A. FRASER ROBERTS reminded the audience of the general principles of Mendelian inheritance as applied to man and simplified the task of his successors by defining such terms as dominant and recessive, autosomal and sex-linked, homozygous and heterozygous, gene frequency, penetrance, and phenocopy.

Dr. J. N. WALTON described the genetics of muscular dystrophy and related disorders, based on an extensive survey in northern England. Clinical and genetic descriptions could not yet be dovetailed, and he thought that a clinical classification was still the best. He recognised the severe Duchenne type, usually sex-linked recessive, rarely autosomal recessive; the limb-girdle type, usually autosomal recessive, sometimes dominant or sex-linked recessive; the facio-scapulo-humoral type, usually dominant and in which abortive cases were common; and the distal benign type, usually dominant.

Dr. E. T. O. SLATER described the methods by which the genetics of mental disorder had been studied, with particular reference to schizophrenia. The high concordance for identical twins—76% in a series of schizophrenics from the Maudsley Hospital and an even higher figure in an American series—indicated the importance of genetic factors in this disease. Family studies confirmed the essential homogeneity of the clinical variations of the disorder. The proportions of first, second, and third degree relatives affected were all appreciably higher than in the general population, but did not fit any simple Mendelian hypothesis. But the family data could be explained by a model in which a single gene was responsible, causing schizophrenia in 100% of homozygotes and in about 20% of heterozygotes.

Dr. C. O. CARTER discussed the information available on the genetics of some of the common malformations, which were now a major cause of infant deaths. Only one of the commoner malformations—namely, mongolism—was purely genetically determined. Similarly malformations purely environmentally determined—for example, those following rubella in pregnancy—were also uncommon. For most of the common malformations there was evidence of a mixed genetic and environmental ætiology. This was the case for congenital pyloric stenosis. The sex ratio of 5 male to 1 female affected, and new family data indicating that an especially high proportion of the relatives of the female index patients were affected, suggested that the predisposing genetic constitution was a dominant gene acting on a sex-modified multifactorial background. The biological nature of the genetic and environmental factors in this and other common malformations was usually not known. But in congenital dislocation of the hip there was evidence for a specific environmental factor—intrauterine posture—as well as two sets of genetic factors, one affecting the development of the acetabulum and the other the laxity of all joints.

CHROMOSOME MUTATIONS

Dr. C. E. FORD described the human chromosomes and the methods now available for their culture and identification. The most recent technique, that of culturing leucocytes from peripheral blood, was satisfactory, but it was often wise to culture more than one tissue. The mechanisms by which chromosome anomalies could arise were lagging of chromosomes at cell division, non-disjunction, abnormal spindle formation, chromosome division without cell division, fragmentation leading to reciprocal translocation, inversion, duplication, and deficiency.

Prof. PAUL POLANI described the sex-chromosome anomalies found in phenotypic females. Most chromatin-negative patients with ovarian dysgenesis, with or without webbing of the neck, had 45 chromosomes and the genetic constitution XO; a few were mosaics. Some chromatin-negative females with "pure gonadal dysgenesis" may have an XY chromosone constitution. The puzzling group of patients with ovarian dysgenesis who are chromatin-positive (none of these have webbing of the neck) are a mixed group. Some are mosaics XO/XX, XO/XXX, or even XO/XX/XXX; some have a single X and a large chromosome—possibly an isochromosome of the long arm of the X. Cases of testicular feminisation are due to a gene mutation, and, though phenotypically female, are all XY.

Dr. W. M. COURT BROWN discussed the sex-chromosome abnormalities found in phenotypic males. Individuals with the genetic constitution XXY were males, but always had testicular atrophy; abnormal hair distribution, gynæcomastia, and mental retardation were less constant features. The masculinising effect of the Y chromosome was seen even in individuals who were XXXXY. In mosaics the ratio of cells of each type might vary in different tissues. In one case blood-cultures showed a normal XY genotype, but skin cultures showed an XO/XY/XYY mosaicism. Recent surveys in Scotland had shown 9 sex-chromosome abnormalities in 2500 boys; 3 were mosaics and the remainder XXY.

Prof. L. S. PENROSE described the chromosomes in mongolism. The incidence of mongolism in maternity-hospital surveys was between 1 in 600 and 1 in 700. This had been confirmed by whole-population surveys in Denmark and Victoria, Australia. Mother's age suggested a distinction into group-A mongols, independent of maternal age, and group-B mongols, who were increasingly common as the mother aged. The standard genotype for mongolism was 47 chromosomes with trisomy of chromosome 21. But translocation mongolism, with 46 chromosomes but a 15/21, 21/21, or 22/21 translocation, was important in explaining some at least of the instances of several mongols occurring in a family.

Dr. M. FRACCARO described some of the other autosomal aberrations that had been reported. A syndrome was in process of being identified with trisomy of a chromosome in the 16 to 18 range. The syndrome included low-set ears, micrognathia, webbing of the neck, a congenital heart defect, and mental retardation. Another syndrome was probably associated with trisomy of a chromosome in the 13 to 15 range, including harelip and cleft palate, polydactyly, congenital heart defect, and bilateral colobomata.

BIOCHEMICAL GENETICS

Prof. C. E. DENT gave examples of the use of urinary chromatography for the discovery of metabolic errors. There are traces of some 40–50 aminoacids in normal urine. In cystinuria the " spot " for cystine is easily recognised as being much too strong. There are at least two cystinurias—one in which cystine alone is raised and another, the Fanconi syndrome, in which cystinuria is associated with more generalised aminoaciduria. The Fanconi syndrome can be subdivided into conditions with and without congenital cirrhosis of the liver. In the latter a tyrosine spot is pre-eminent. Garrod's original concept of the missing enzyme can be widened. In some instances the enzyme may not be merely missing, but be replaced by another, abnormal one. The polymorphism seen for the hæmoglobins could be the pattern. Xanthine oxidase is the enzyme which converts both hypoxanthine into xanthine and xanthine into uric acid. Yet in xanthinuria only the second step is absent. One has to assume a " half-enzyme abnormality ".

Prof. H. HARRIS chose suxamethonium apnœa as an example of genetically determined drug sensitivity. The drug is used as a short-term muscle relaxant in anæsthesia. Its action is brief because it is inactivated by the plasma-enzyme, pseudocholinesterase. Some patients develop a much prolonged paralysis because the enzyme level is low. Examination of their relatives led to the discovery of more individuals with a deficiency of the enzyme. By the use of the pseudocholinesterase inhibitor, dibucaine, the members of these families could be separated into three groups corresponding to abnormal and normal homozygotes and to heterozygotes. In normal persons a given concentration of dibucaine caused about 80% inhibition, but in the abnormal homozygotes the inhibition was about 20%, and in the heterozygotes it was intermediate between these two. There was no overlap of the three ranges of inhibition. There were obviously two enzymes of which one was less efficient in hydrolysing suxamethonium than the other. Use of another inhibitor, sodium fluoride, allowed distinction of yet another type of genetically determined pseudocholinesterase.

Prof. C. H. BURNETT (North Carolina, U.S.A.) described the mode of inheritance of vitamin-D-resistant rickets. The condition is due to a dominant sex-linked gene. If the proband is a man he will be found to transmit the disease only to his daughters, whereas a woman can have both affected sons and daughters. Men are more severely affected than women, who may often show merely hypophosphatæmia without clinical disease. Thus the gene is not fully dominant, and the inheritance of a normal X chromosome together with the abnormal X chromosome will modify the effect of the latter.

Dr. H. LEHMANN described the four peptide chains which are found in human hæmoglobin. There are three hæmoglobins—the major adult pigment hæmoglobin A, the minor component hæmoglobin A_2, and in infants fœtal hæmoglobin F. All three are under independent genetical control. Of the four peptide chains the α-chain was present in all three and was combined with β-chains in hæmoglobin A, with δ-chains in hæmoglobin A_2, and with γ-chains in hæmoglobin F. Thus a mutation of the α-chain will result in variants of A, A_2, and F. Mutation of the β-chain will only affect hæmoglobin A, of the δ-chain hæmoglobin A_2, and of the γ-chain hæmoglobin F. Deficiency of the α-chain will cause the surplus β-chains to form a β-chain tetramere β_4 or hæmoglobin H, and surplus γ-chains formed γ_4 or hæmoglobin Bart's. When an abnormal β-chain hæmoglobin was inherited together with an abnormal α-chain hæmoglobin, four adult hæmoglobins were found in the phenotype because the normal α-chains of the first pigment and the normal β-chains of the second combined to form hæmoglobin A, and the abnormal α- and β-chains combined as a doubly abnormal hæmoglobin. There were two types of thalassæmia, one affecting the α-chains and one depressing the production of β-chains. The second could only lower the synthesis of hæmoglobin A, and in this type hæmoglobin F and hæmoglobin A_2 were raised.

CLINICAL PROBLEMS

Dr. R. B. MCCONNELL discussed heredity and the alimentary tract. Though there was no evidence for genetic factors in the causation of carcinoma of the pancreas, the rare cases of the disorder in association with tylosis, of which 19 instances had been found in two families in the north of England, were due to a dominant gene. Fibrocystic disease of the pancreas was determined by an autosomal recessive gene; but its frequency, perhaps 1 in 2000 births, suggested that the gene might be advantageous in the heterozygote. Duodenal ulcer afforded an example of a condition determined both by environmental and by genetic factors, probably multifactorial. The incidence in group-O non-secretor individuals was 2·4 times that in non-O^2 secretor individuals and these differences in susceptibility had been found in several different races.

Dr. R. T. C. PRATT gave some examples of the part played by heredity in neurology. In gargoylism the genetic distinction into autosomal and sex-linked recessive pedigrees had led to the finding of clinical differences between the two types—for example, clouding of the cornea is absent in the sex-linked recessive cases, but deafness is relatively common. In multiple neurofibromatosis genetic studies had clarified the significance of café-au-lait spots. Similar spots were seen in normal individuals, but if more than 6 such spots of more than 1·5 cm. in diameter were present this was good evidence that the individual had the gene for multiple neurofibromatosis. A study of the children of sporadic cases of multiple neuro-

fibromatosis had shown that these sporadic cases were not phenocopies, but could all be attributed to fresh mutations.

Dr. FRASER ROBERTS discussed the problems of giving genetic advice to parents. This usually involved advising parents who had one abnormal child of the risk that a further child would be affected in the same way. He had no doubt that the medical profession had a duty to attempt to give advice on such matters when patients asked for it. All too often the parents would receive plenty of advice from others less qualified to give it. The duty was to give advice: any decisions must rest with the parents. A first essential for giving advice was to have an accurate diagnosis. If the genetics of the condition were known, though it was important to remember that apparently similar conditions could be determined by more than one gene, it was often possible to give exact odds. Where the genetics were not known, or were complex, there were often empirical-risk figures to act as a guide, and fortunately, in general, the more complex the genetics the less the risks.

Dr. C. A. CLARKE, summing up, discussed some of his difficulties in attempting to apply genetics to medicine. He felt that we should by now know more examples of heterozygote advantage to explain the many genetic polymorphisms in man. He found it difficult to know, in genetic studies, what were the best controls; for example, in relation to ABO groups and peptic ulcer, were the patient's own sibs better than the general population? He was appreciative of the work of the biochemical geneticists, but found it difficult to visualise the connections between an enzyme alteration and Hapsburg lip.

RHEUMATOID ARTHRITIS

A MEDICAL-ORTHOPÆDIC symposium on Rheumatoid Arthritis was held by the Empire Rheumatism Council in London on March 3.

REST *versus* EXERCISE

Dr. J. J. R. DUTHIE (Edinburgh) described a controlled clinical trial designed to compare the progress of two groups of patients in one of which all affected joints were immobilised for four weeks, the other receiving more orthodox treatment with rest splinting only. After four weeks both groups had the same treatment. 68 patients—34 in each group—were now in the trial, and 45 had already been followed for a year. The period of immobilisation was followed by some loss of movement, but this was soon regained and at six months 28% of the patients initially immobilised were in the top functional grade compared with only 19% in the control group. The disease was inactive in 38% of the immobilised group, compared with 18% of the controls. This advantage was maintained in those followed for a year. In 6 elderly patients in the immobilised group respiratory infections or thrombotic complications developed. Immobilisation did not lead to loss of function and was sometimes beneficial, though it was not without risk to elderly people.

Dr. K. BERGLUND (Stockholm) said that vigorous exercise was accepted as the basis of treatment in Stockholm, and, though there were no controlled studies to support this, he thought that local injection of corticosteroids reduced inflammation as effectively as rest. Dr. DUTHIE replied that local steroid treatment was a very artificial way of arresting inflammation and there was evidence that repeated injections could damage a joint. Dr. A. G. S. HILL (Aylesbury) said that, although the risk of immobilisation was not as great as previously thought, it was probably accentuated when there was much loss of cartilage. Dr. G. D. KERSLEY (Bath) stressed the difference between the treatment of rheumatoid arthritis and of ankylosing spondylitis, where rest had a harmful effect. Prof. J. H. KELLGREN (Manchester) pointed out that rheumatoid joints were often unstable rather than stiff. The unstable group was suitable for splintage, but he was not so sure about the others. Mr. W. J. W. SHARRARD (Sheffield) said that treatment at present was often a paradoxical mixture of rest and exercise. He and other speakers emphasised the importance of treating each joint selectively, resting it during disease activity and muscle spasm and using movement as activity subsided.

ORGANISATION PROBLEMS

Mr. W. D. COLTART, discussing the general indications for surgery in rheumatoid arthritis, spoke of the importance of collaboration between rheumatologists and orthopædic surgeons. Standard orthopædic procedures were as successful in rheumatoid arthritis as in any other condition, but, in planning surgery on a single joint, the functional condition of other joints—either involved at the time or perhaps to become so in the future—had to be considered together with the state of the patient as a whole. He confessed that orthopædic surgeons were no longer capable of managing rheumatoid patients and there was a considerable need for rheumatology units in centres which already had departments of orthopædics and physical medicine.

Professor KELLGREN declared that the problem of surgery in rheumatoid arthritis was not clinical but organisational. On the background of a complex regimen of medical care, a time would come when elective operation was desirable without interrupting this regimen. At present this was often difficult. Three people were necessary: the physician-rheumatologist, the orthopædic surgeon, and the expert in rehabilitation and physical medicine.

Prof. S. J. HARTFALL (Leeds) also spoke of the importance of assessing the total patient; the most disastrous cases were those of bad selection. Other speakers agreed with the need for teamwork in suitable centres, of which only a handful were available in this country.

SYSTEMIC STEROIDS AND SURGERY

Dr. MICHAEL WELLS had used S.U.4885 ('Metopirone,') an adrenal inhibitor, to measure pituitary function in response to stress and shown that systemic corticosteroid therapy suppressed the pituitary response rather than that of the adrenal gland, which, in fact, usually showed a satisfactory if slightly delayed response to exogenous corticotrophin after or during long-continued corticosteroid treatment. The duration of diminished pituitary response had not been defined: it had been demonstrated after only two weeks' treatment and could persist for up to two years. It was therefore necessary not only to continue systemic corticosteroid treatment during surgery but to give booster doses to cover the period of stress. A suitable scheme was intramuscular cortisone acetate 100 mg. twenty-four hours before surgery, 100 mg. on the day of operation, and 100 mg. the day after, together with oral corticosteroids. The idea that corticotrophin could be used to "reawaken the adrenals" was now obviously fallacious. Systemic steroids had no adverse effect on wound healing except in very high dosage, though (especially with triamcinolone and dexamethasone) they did cause atrophy of dermal collagen leading to bruising and ulceration. Skin sutures readily cut through such atrophic skin.

Dr. C. F. SCURR said that acute circulatory collapse could follow even minor surgical procedures in these patients, and, although it usually responded to intravenous hydrocortisone, prophylactic corticosteroid treatment was essential. A treatment card should always be carried by patients on steroid therapy. (Other suggestions included neck or wristlet discs so that the need for steroid replacement would be quickly noticed after road accidents, &c.)

Several speakers emphasised the need for greater knowledge of adrenal collapse. What was the blood-cortisol level during these attacks? What was the place of aldosterone and noradrenaline? How was it that many patients who had been on long-term steroids went successfully through severe operations, although not given prophylactic steroid replacement?

The orthopædic surgeons present agreed that there was no delay in soft-tissue healing with long-term steroids, though there was some disagreement about bone union. Skin closure was sometimes difficult because of sutures cutting through.

OPERATIVE PROCEDURES

Mr. R. G. PULVERTAFT (Derby) described the surgery of the hand and wrist. The most useful operations were the release of

snapping tendons, grafting or transference of ruptured tendons, arthroplasty for early ulnar drift, and joint arthrodesis, the advantage of the last being that the exact results could be anticipated. The "swan-neck" deformity, with extension of the proximal interphalangeal joint and flexion of the distal interphalangeal joint, was due to rupture of the long extensor tendon and was best treated by early tendon repair, or, later, by arthrodesis. Mr. NORMAN CAPENER (Exeter) demonstrated a number of appliances, but he stressed that they were incidental rather than definitive in the treatment of rheumatoid arthritis. For splintage, plaster was excellent with its even support and warmth; and Mr. Capener also described the use of block leather and mobile spring splints. Plastic splints were no substitute for plaster—they did not fit so well and were not porous. Professor KELLGREN said that palmar subluxation of the metacarpophalangeal joint was the most important deformity in the rheumatoid hand, ulnar drift and contractures being secondary to this. The mechanism of ligamentous relaxation was quite unknown. Diffuse flexor-tendon lesions were commoner than snapping tendons and were best treated with local hydrocortisone. Many pathological changes were reversible as the disease became quiescent.

Mr. D. L. SAVILL (Edinburgh), discussing minor orthopædic procedures, mentioned the Riordan technique of joint injection with nitrogen mustard, which was said to lead to disappearance of plasma-cells. The carpal-tunnel syndrome, common in rheumatoid arthritis, was effectively treated by division of the transverse carpal ligament. Other useful procedures were synovectomy of the metacarpophalangeal joint, excision of granulation tissue from the dorsum of the wrist, and, in the feet, excision of the proximal phalanges or metatarsal heads and amputation of toes through metatarsal necks. Arthroplasty of the elbow with removal of the radial head produced a useful increase in range of movement and rotation. Arthrodesis of the wrist-joint was regarded by Mr. J. C. R. HINDENACH and Dr. OSWALD SAVAGE as among the most useful operations in rheumatoid arthritis.

Mr. JOHN CHARNLEY (Manchester) described a new mechanical arthroplasty for the hip, in which a metallic prosthetic replacement of the femoral head, cemented in the shaft of the femur so that the weight load was widely distributed, worked with extremely low friction resistance against a socket of inert "Teflon" lining the acetabulum. In 75 operations since January, 1960, the results had been far superior to those of any other comparable procedure; and, owing to the resulting absence of pain and remarkable range of movement, this operation was particularly suitable for severely disabled patients with rheumatoid arthritis. Mr. I. S. SMILLIE (University of St. Andrews) reviewed surgery of the knee-joint in rheumatoid arthritis and discussed the indications for synovectomy, debridement, linear osteotomy of the tibial head, arthroplasty, and arthrodesis. Mr. GEOFFREY PLATT (Aylesbury) presented his own series of cases of knee arthroplasty: the result was a stable joint with a limited but useful range of movement.

CERVICAL SPINE

Dr. JAMES SHARP (Manchester) said that the apophyseal joints and intervertebral discs of the cervical spine were affected in 40% of hospital patients with rheumatoid arthritis. The features were disc narrowing especially in the upper vertebræ, radiological erosions rather than sclerosis with little osteophytosis, and subluxation seen best in films taken in flexion. Painful neck stiffness and referred pain were no guide to the degree of instability and were usually controlled by supporting collars. The main hazard was damage to the cervical cord and medulla, leading by slow progression to gross tetraplegia and sensory loss. Such cord damage was an absolute indication for reduction of the displacement by skull traction and surgical stabilisation of the cervical spine. This was usually followed by regression of the neurological signs, even if they had been present for many months.

NEED FOR NEW CENTRES

Closing, Dr. HILL returned to the integration of medical and surgical management of rheumatoid arthritis. Joint medical and orthopædic consultation in suitable centres was necessary, and the facilities in this country were quite inadequate for the estimated $1\frac{3}{4}$ million people with rheumatoid arthritis and $3\frac{1}{2}$ million with degenerative joint-disease. New units should be established, staffed by young men trained at the few already in existence.

Parliament

National Health Service Prescribing

ON March 15 Mr. ENOCH POWELL, the Minister of Health, made the following statement in the House of Commons:

The Secretary of State for Scotland and I recently asked the Standing Joint Committee on the Classification of Proprietary Preparations, of which Lord Cohen of Birkenhead is chairman, to consider if they could help doctors in prescribing by giving more guidance on proprietary preparations. The Committee has now reported and it advises that, while there should continue to be no absolute restriction on the prescribing of any drug which the doctor considers necessary for the treatment of his patient, he need not normally go outside the drugs and preparations described from time to time in the *British Pharmacopœia*, the *British Pharmaceutical Codex*, and the *British National Formulary*, together with the drugs that the Committee classify as N (new drugs of proved value not yet standard), and P (drugs for which there is prima-facie evidence of therapeutic value but where the Committee want further evidence before firm classification). The report goes on to advise that a doctor who prescribes other preparations may be liable to be called on to justify his action if the cost of his prescribing is being formally investigated. The report will be published and, in consultation with the medical profession, will be brought to the attention of all doctors.

My right hon. Friend and I are aware that the pharmaceutical industry may be apprehensive of the effect of this advice on its future progress and development; but we are sure that any such apprehension would be ill founded. Many standard preparations are, and will no doubt continue to be, available only in proprietary form, or cost little more or no more in proprietary than in unbranded form. This, together with categories N and P, and the individual doctor's professional discretion, will continue to provide full scope for the products of the industry's research and development to find their reward.

QUESTION TIME

Cost of Standard and Proprietary Drugs to the N.H.S.

The total cost to the Exchequer in the past four years of prescriptions dispensed by chemists in England and Wales was approximately:

	Prescriptions specifying drugs by standard names	*Prescriptions specifying drugs by proprietary names*
	£m.	£m.
1956	16·6	30·8
1957	13·2	34·8
1958	13·9	38·6
1959	13·9	45·2
1960	14·1	50·7

Rather less than half, by value, of the drugs prescribed by standard names in 1959 and 1960 were available only as proprietaries. The proportion for earlier years is not known.

Work Study in the Hospital Regions

The regional hospital boards now employ 36 full-time work-study specialists; 27 have been appointed in the past six months.

Leprosy in the United Kingdom

There were 248 cases of leprosy in Great Britain at Dec. 31, 1960, compared with 212 at Dec. 31, 1959.

Aliens and the N.H.S.

In 1960 nine foreigners were refused leave to land in the United Kingdom because their sole object was to obtain free medical treatment.

In England Now

A Running Commentary by Peripatetic Correspondents

MY patients often tell me that "it's wonderful what doctors can do nowadays"; but sometimes I wonder if they really mean it.

"No, thanks, doctor. I've got plenty of all the kinds of tablets left. Well, no, I don't take half what they tell me to at the hospital. They make me so dizzy all the time, and I've got my work to do."

"Well, I got so fed up with asking off from work to go to the hospital week after week, twice a week, and Bill Timmins who works along of me he says, 'Tom, why not give bone-setter in Taviton Street a try', so I went along. Directly he sees me come in at the door he says, 'I can see one thing that's the matter with you, my lad.' 'Oh, what's that?' I said, curious-like. 'You've got one leg shorter than the other,' he says. Then he gets me on his couch and measures me up, and right enough my left leg was a good inch shorter than the right. He felt around my back, and found it was because three little bones was out of place. Suddenly he lifts me up, and with me almost standing on my head he gives my left leg an almighty twist and something went crack all in my back. 'That's got it!' he says, 'you can go now.' And he'd done the trick, right enough. Never had an ache nor pain since."

"No, I didn't actually go back to the psychiatrist again, doctor. Them feelings went out of my head, thank goodness. You know, me and Bert Watkins from the boiler shop, we got to looking over the *Mirror* together one 'ten-o'clocks' and we found we was both under Taurus. 'Today holds out great promise for affairs of the heart,' it said."

* * *

We had heard a fascinating lecture on a rare industrial disease caused by tin, and followed wide-eyed the clinical trail which ended at the tin-mine in Bolivia. What fun, we thought, to find a disease that justified such an expedition. If only we... But would it not be more logical to decide first where we should like to go, and then find the disease?

"The Friendly Isles," said Freddie. "Such a change from dirty Heparport. Ideal climate. Queen Salote..."

"Giant tortoises," I suggested. "Tortoiseshell. Spectacle frames. Glabellar dermatitis."

The school medical authorities were very cooperative. They had a lot of schoolchildren. An incredible number wore glasses. National Health frames. No tortoiseshell.

The expensive schools were more coy but eventually agreed. Plenty of spectacles. Lots of tortoiseshell. And—eureka!—six cases of glabellar dermatitis.

Spectacle-frame manufacturers were very cooperative. Tour of works. Dinner with directors. Made a splendid colour film of the whole process. Showed it to the firm. Another dinner with the directors. After the second glass of port Freddie pitched in. "I've been thinking," he mused, "if tortoiseshell can do this to the bridges of human noses, I wonder what happens to the backs of tortoises' necks. Now if we were to go and see... Good heavens, are you ill?"

The managing director appeared to be having an apoplectic fit, but had in fact been convulsed with laughter in mid-swallow. When he recovered, he explained.

"Your task is much simpler than you feared, my good Sir," he said. "This tortoiseshell is made of plastic. Occasional skin allergies well known. Made by Messrs. X at their Heparport factory."

* * *

The Royal Moroccan Army is French trained, and smartly clothed in khaki battle-dress and bright green berets. It looks quite effective for its purpose—whatever that may be. At the invitation of their English civilian medical officer I attended sick-parade at the barracks of the 4th Cavalry Regiment one morning, curious to see how this ceremony compares with our own. The M.O. is a charming, if unexpected product of Eton and Oxford, and modestly attributes his appointment to his prowess at polo, which he introduced into the Moroccan Army with great success.

There seemed to be a striking number of digestive disturbances of various sorts, which may well have been initiated or exacerbated by the month-long fast of Ramadan, during which all Moslems are prohibited from eating or drinking between sunrise and sunset. This means that they have a meal at bedtime and another at 3 A.M., so they go short of sleep too. There were several cases of lumbago, and two of sciatica, which perhaps was to be expected among cavalrymen. Then came several children, all with diarrhœa and vomiting. They were encased in many layers of warm clothing which they wear all through the summer, but it seemed quite clean. There were a few boils, cuts, and sprains, too. The most tragic case of the morning was a swashbuckling negroid sergeant, the horse-master of the squadron and a chief mainstay of the polo team. He had developed a widespread and painful eczematous skin sensitivity to horse-hair—and the season was only in its first week.

* * *

We must be a rather backward area, medically speaking. During and immediately after the war the proximity of a number of military establishments produced a steady flow of enthusiastic medical officers who swelled any medical meetings which were arranged. Since 1946 some half-dozen attempts have been made to revive these meetings. So far they have failed miserably, and some blame the honorary secretaries who should organise the meetings; but when I look at my own life the explanation is clear.

On Monday evenings I try to catch up with the general lack of education which resulted from my "first M.B. from school", and I go with my wife to evening classes on modern art. On Tuesday evenings I join a study group doing research on British wild mammals. On the last Wednesday evening in each month I go to join my specialist colleagues in the Midlands for a clinical meeting in the nearest provincial city. On Thursday and Friday evenings some of my children are late from school because of various extracurricular activities, and I go along to collect them, because they have up to two hours of homework to do when they get home. At weekends there is the taxi service to be maintained on a rota system with other parents to and from parties, to say nothing of the one or two weekends each year spent on postgraduate courses. By the time we have had the odd couple in to supper there is no room in the diary for local evening clinical meetings. Even the television set has been banished from the drawing-room: the children tell me that it still works. Having watched so many people "go to pieces" on retirement, I have learnt how important it is to have some other interest on which to fall back when I retire (in 25 years' time). I only pray that my interest in medicine will last out until then.

* * *

Shades of Pilkington grave and gay
  How lucky you are to get your pay.
You'll change your car and settle your bills
  And all your other outstanding ills.

But in this small East Anglian town
  That considers itself of high renown
We work for a Varsity old and staid
  And know that we shall never be paid.

There's talk of stipends—an equal share,
  But we know that the "perks" aren't equal where
There are college fellowships rich and fat
  And supervisions and things like that.

And some are television stars
  And talk on history or life on Mars
(Or even the shape of a Grecian vase).
These are the fellows who voted away
  Somebody's else's extra pay.

Letters to the Editor

"A DEPARTURE FROM NORMAL PRACTICE"

SIR,—The case of Landau *v.* Werner, reported on p. 610 last week, raises issues important to many psychiatrists and perhaps to the whole profession.

All psychiatrists doing outpatient work, or private practice, meet many frustrated and lonely patients. So do general practitioners.

In any treatment, however superficial, an emotional attitude to the doctor may arise in the patient: this may be one of simple confidence, or something much deeper, which will be regarded as transference by a psychiatrist but as falling in love by a patient who has not had the benefit of a psychiatric education. This will happen to general practitioners as well as to psychiatrists. At all stages the doctor must be aware of the situation, and has a choice between using the relationship for the patient's benefit, or attempting to reduce it, which may entail breaking off the case.

If he breaks off, he knows that this rejection may leave the patient worse than he found her, and perhaps incurable and sometimes suicidal. We may ask, what would be the attitude of a court to a doctor who knowingly inflicts this harm? In any case, whatever the legal position, any responsible doctor will certainly feel a considerable moral responsibility and a challenge to his conscience.

For this reason, and because this relationship is an important therapeutic instrument, the doctor has generally chosen to go on with the case. He has realised that, in so doing, he is running the risk of professional embarrassment, and undertaking (to say the least), an exacting, time-consuming, and often unrewarding task. He has also felt the need to try to help cases of greater difficulty, such as schizophrenics and homosexuals; the risks of which are even greater.

Following the judgment in Landau *v.* Werner, his risks are now greatly increased (a) because certain patients will be more ready to bring actions against doctors (and some surgeons may see parallels to litigation after operations here); and (b) because bankruptcy may follow from what the court holds to be a professional mistake, even when this was explicitly stated to have been made in good faith and without professional misconduct of any kind.

If a patient deteriorates under treatment, it may be very difficult, even for doctors, to decide how much of this deterioration has been due to the illness and how much to the treatment. Yet a precedent has now been set for this assessment of this vital point to be made by the court, without even the help of a medical opinion based on recent examination. (This is, of course, quite distinct from assessment of the extent of the disability in financial terms, which, though it may be a legal question, is neither a medical nor a scientific one.)

One safeguard for the doctor may be to try to avoid all social contact. In practice, this is often very difficult; in full-scale analysis, it may be possible, but in other cases the doctor may feel he needs to supplement his efforts (which must be very limited in time) by encouraging social activities in his patient. His only weapon in doing so may be his emotional relationship with the patient. Indeed there are risks. But it would not be hard to enumerate patients who today are alive, well, and earning as a result of such measures, but would be dead, sick, or disabled without them.

Yet the penalty of what the court holds to be an error of judgment may be bankruptcy. Even if the case is undertaken by a defence society, the doctor suffers considerable damage to his reputation, while fellow members of his profession have to pay a substantial bill—not only in damages but even more in costs.

ROGER TREDGOLD
KENNETH SODDY.

London, W.1.

HEAVY WORK IN EARLY PREGNANCY

SIR,—When a pregnant woman first attends an antenatal clinic a history is taken, often by a very junior member of staff, sometimes by someone more senior. Whoever does this first questioning is usually rushed—scarcely surprising as there are nearly a million women in early pregnancy in England and Wales in any one year—and in consequence seldom has time to do more than record salient facts; the woman, too, gets a sense of this rush and, anxious not to be a nuisance, leaves many questions unasked.

In a detailed study (sponsored by the National Spastics Society) of pregnant women attending hospital antenatal clinics early in pregnancy, time was set aside specifically for a personal interview with each patient, in addition to the routine of medical examination, blood-tests, and "booking in". This personal interview was arranged on the same day as the booking if the patient had travelled far or otherwise a few days later. The latter arrangement was much to be preferred, because when the interview was on the same day as the booking visit the busyness of the clinic made it much more difficult to get from her the necessary information. Seemingly the business of being "booked" filled the mind so full of new thoughts that personal problems were pushed temporarily into the background. By contrast when the special interview was held in a quiet room a day or so after booking there was a relaxed atmosphere far removed from the somewhat overwhelming and frightening reality of the hospital clinic. Questions and answers were easily exchanged, and an atmosphere of mutual trust created.

So far 510 women have been questioned by one of us (R. W.); the results will be reported. Among the questions was one about the woman's employment during pregnancy; and the answers were classified as part-time some days, part-time every day, full-time medium, and full-time heavy.

It appears to be accepted that women having their first baby continue working for part, if not all, of their pregnancy; and such work, provided it is no great strain and does not interfere with health, is probably desirable. Very heavy work cannot be desirable in pregnancy; yet we found a surprising number of women working very hard and not thinking of easing up even though this was not specially difficult; it just had not occurred to them to live more quietly.

Four case-records illustrate this.

CASE 1.—A young woman seen early in pregnancy who had had 2 previous abortions worked for 8 hours a day at a treadle sewing-machine. She could easily have changed to an electrically-driven machine, but she had never thought of this. She took our advice, and curtailed her activities; she carried her baby successfully to term.

CASE 2.—A 36-year-old primigravida with a history of 7 years' infertility was a long-distance lorry driver; she was seen early in pregnancy. When questioned about her work, she said it was easy enough in summer, but a bit rough in winter when the lorry became stuck in the snow. She was perfectly willing to give up her work during pregnancy.

CASE 3.—A 37-year-old primigravida who had not conceived for 12 years was seen when 8 weeks pregnant; she had already bled. She managed her mother's fish-and-chip shop, even though any of her 5 sisters could easily have taken over; she simply had not considered taking life more easily.

CASE 4.—This patient had had 2 abortions; she came to the clinic at 6 weeks. She had just bought her own shop and was running it single-handed. When told how desirable and necessary was more rest in early pregnancy, she was clearly greatly surprised.

It will be seen that many women, including even those with previous longstanding infertility, those who had had abortions, and those with pregnancy bleeding, were engaged in heavy work. We believe all pregnant women

should be asked their occupation so that those doing unsuitable work should have some of their activities curtailed.

Department of Obstetrics and Gynæcology, University of Sheffield.

C. S. RUSSELL
R. WALTON.

MAURITIUS AND MALTHUS

SIR,—I must disagree with you when you state in your leader on the situation in Mauritius (March 11), "Family planning seems the only answer."

Many experts on population consider that the world will be able to support a much increased population, and that the problem is essentially one of distribution and development. This does not make the problem any less, but does, I submit, take it out of the realm of medicine.

I feel that to introduce family planning on a scale large enough to be "successful" will require an immense expenditure of effort, money, and time. This will achieve nothing positive; would it not be better to expend them on improving education, agriculture, and transport in the poorer areas?

Malthusianism, I would suggest, has merely provided the more prosperous with plausible excuses for shirking their responsibilities towards the less fortunate.

Dorking. ROBERT J. BAKER.

LEAD POISONING FROM LEAD-GLAZED POTTERY

SIR,—The article by Mr. Whitehead and Dr. Prior [1] prompts us to describe the problem of lead-poisoning from the same source among peasants in Yugoslavia.

Our recent experience demonstrates that this is again a serious public-health problem. Within the short space of six years we have treated over 40 patients with severe lead poisoning, including 3 cases of encephalopathy (1 died), and 6 cases of lead palsy. In Yugoslavia many peasants still use lead-glazed pottery,[2] and lead poisoning is more frequent in winter when peasants boil wine and keep pickled cucumber in these vessels—i.e., when they themselves carry out the test prescribed by our Food Control Act [3] for determining the lead content of the glaze, by boiling acetic acid in the lead-glazed earthenware! After all, as early as 1754 James Lind had recorded that preparing fresh lemon juice "in a glazed coarse earthen vessel" led to very serious lead contamination.[4] Acid food-ingredients kept or boiled in lead-glazed earthenware containers extract lead from the glaze until none is left; because of this we disagree with Whitehead and Prior and consider that lead contamination is more appreciable *before* the glaze becomes cracked and broken.

Not long ago Sverdlov [5] reported that in Russia, too, lead poisoning from lead-glazed earthenware is very frequent. He stated that to make a small earthenware pot or jug about 20–30 g. of lead was used. The results of lead-content determinations on earthenware by Whitehead and Prior and also by one of us [6] indicate that these vessels contain about the same amount of lead in different countries. No wonder, therefore, that this kind of earthenware, wherever used, represents a health hazard.

Judging by the appearance of a report from Whitehead and Prior in England and from Sverdlov in Russia in the same year, and taking into account the poisonings due to the same cause in Yugoslavia, the old saying of Ramazzini [7] that "*metallicæ pestes*" can be encountered in any country where pottery is carried on still holds good. The many different countries in which this kind of poisoning can be found even today seems to provide the answer to Ramazzini's rhetorical question: "*Quæ enim civitas, quod oppidum, in quo figlina artium antiquissima non exerceatur?*"*

Long ago *Pictones* (the inhabitants of the French province of Poitiers) and *Damnonii* (the inhabitants of Devonshire in England) figured in the names of an enigmatic disease ("*Colica Pictonum*" and "*Morbus colicus Damnoniorum*") simply because in their regions the method of wine-making led to its heavy contamination with lead. The ætiology of the disease has long since been explained; but even today the reason why it occurs sometimes puzzles us.

Institute for Medical Research (incorporating the Institute of Industrial Hygiene), Yugoslav Academy of Sciences and Arts, Zagreb. TIHOMIL BERITIĆ.

"Andrija Štampar" School of Public Health, Medical Faculty, University of Zagreb. DUNJA STAHULJAK.

1. Whitehead, T. P., Prior, A. P. *Lancet*, 1960, ii, 1343.
2. Beritić, T. *Liet. jug. Akad. Znan.* 1956, **61**, 363.
3. Beritić, T., Djurić, D. *Higijena*, 1956, **8**, 12.
4. Lind, J. *Scots Magazine*, 1754, **16**, 227. Cited by Meiklejohn, A. *Brit. J. industr. Med.* 1954, **11**, 40.
5. Sverdlov, S. L. *Soviet med., Moscow*, 1960, **24**, 135.
6. Beritić, T., Fališevac, J. *Arch. Toxicol.* 1956, **16**, 8.
7. Ramazzini, B. De morbis artificum diatriba; chapter 5. Modena, 1700.

ANTINUCLEAR FACTOR

SIR,—Your interesting annotation of March 11 on the subject of antinuclear factor (A.N.F.) as detected by the fluorescent antibody technique prompts us to discuss a point which has been insufficiently emphasised in articles on this subject [1]—namely, the temperature at which the test is carried out.

Dr. R. G. White [2 3] mentions that temperature may be a critical factor and that many more positive reactions are obtained in the A.N.F. test if sera are left on the tissue overnight at 4°C. He and most other authors carry out the test at room-temperature (20–22°), without specifying any precautions with regard to the temperature of the serum.

The possibility that the effect of temperature might lead to errors in the interpretation of A.N.F. tests led us to carry out the test on a series of control sera at 4°, 20°, and 37°. The sera were taken from pregnant women and mixed hospital patients without collagen disease. The results show that whereas all the results were negative when the sera were warmed to 37° and the entire test carried out at that temperature, increasing numbers of sera gave positive reactions as the temperature of the test was reduced:

Degree of nuclear fluorescence		*Number of sera reacting at:*		
		4°	*18–20°*	*37°*
Negative		0	14	33
Weak	±	18	9	0
	+	10	4	0
	+	5	2	0
	+ +	0	0	0

The method of Holborow, Weir, and Johnson [4] was followed, using unfixed frozen sections of human thyroid gland as a nuclear substrate. The sera were applied to sections at the appropriate temperature for ½ hour and the first wash was carried out at 37° in the warm test. The fluorescent conjugate was applied for ½ hour at room-temperature in all tests and the second wash was at room-temperature. Five of the positive A.N.F.s at room-temperature were found in female hospital patients over 50 years and only one was from an antenatal case.

Scoring of Results

Negative = nuclei appear black against the lighter cytoplasm.
± = faint nuclear fluorescence.
Weak + = nuclei stand out green against cytoplasm.
+ = moderately bright nuclear fluorescence.
+ + = very bright nuclei, as in S.L.E.

At 4° none of the sera were completely negative as judged by the strictest criteria, and it was found that sera which were freshly thawed and still cold when applied to the sections gave results comparable to those obtained at 4°, even if the rest of the procedure was carried out at room-temperature. The intensity of fluorescence in these cold tests in no instance approached that observed with systemic lupus erythematosus (S.L.E.) sera. In 22 cases of S.L.E. tested at 37°, 20 stained very brightly and 2 became almost negative. One of these patients had a three-year history of atypical rheumatoid arthritis and L.E. cells have been found on a previous occasion, while the second patient with a negative A.N.F. at 37° had mild systemic manifestations and had been on cortisone for some months

* For what state and what town is there, in which pottery, that most ancient of arts, is not practised?

1. Alexander, W. R. M., Brember, J. M., Duthie, J. J. R. *Ann. rheum. Dis.* 1960, **19**, 338.
2. White, R. G. *Exp. cell Res.* 1959, suppl. no. 7, p. 263.
3. White, R. G., Bass, B. H., Williams, E. *Lancet*, 1961, i, 368.
4. Holborow, E. J., Weir, D. M., Johnson, G. D. *Brit. med. J.* 1957, ii, 732.

when tested. The advantage of conducting the A.N.F. test at 37° is that an unequivocal baseline is obtained when testing control sera. Some cases of Hashimoto's disease, Sjögren's syndrome, and rheumatoid arthritis still gave positive A.N.F. tests when examined at 37°.

The nature of the cold-reacting A.N.F. is obscure and it may not necessarily have immunological specificity. However that may be, more consistently reproducible results would be obtained if the A.N.F. test was done with a full knowledge of temperature effects. Since antinuclear factors are a group of closely related autoantibodies rather than a single factor, these may have variable thermal ranges. By analogy with hæmolytic anæmias in which agglutinins and hæmolysins may be "cold" or "warm", and cold agglutinins of low titre are of less clinical significance than warm type antibodies, it may be that "cold" weak A.N.F. reactions are sufficiently common in healthy subjects to be of little clinical importance and that if the A.N.F. test is carried out at 37° the results would have greater diagnostic significance.

We agree with Friou [5 6] and with Pollak et al.[7] that the test gains in diagnostic value when carried out semi-quantitatively on serum dilutions, since strong positive reactions correlate more closely with the L.E.-cell test and do not occur in diseases unrelated to the group of "autoimmune" collagen diseases.

The antinuclear factors differ not only in their temperature range but also in their reactivity with nuclei. S.L.E. sera produce an overall uniform fluorescence of the nucleus as a rule while other sera, often from patients with Sjögren's syndrome, give a speckled appearance in which only certain parts of the nucleus are stained. The "speckled" reaction may be found in both the "cold" and the "warm" reacting A.N.F., sometimes to serum dilutions of up to 1/1000.

It is interesting to note that when using the Coons sandwich technique for the detection of thyroid autoantibodies no differences were found with variations in temperature between 4° and 37°. This applies equally to cytoplasmic staining due to "microsomal" antibodies and to staining produced by antithyroglobulin or by antibodies to the second antigen of the thyroid colloid (CA2).[8]

Institute of Clinical Research and Courtauld Institute of Biochemistry, Middlesex Hospital, London, W.1.

K. COUCHMAN
DEBORAH DONIACH
I. M. ROITT.

LYMPHADENOID GOITRE AND SYSTEMIC LUPUS ERYTHEMATOSUS

SIR,—I was very interested in the paper by Dr. White and his colleagues (Feb. 18). We have observed a woman with suspected systemic lupus erythematosus who was later found to have myxœdema (not lymphadenoid goitre):

A woman of 53, seen in the outpatient department in 1952, complained of being very tired and listless. She improved dramatically with iron, but relapsed when the treatment was stopped. She also complained of aching pains in various parts of the chest and abdomen, and, apart from a high erythrocyte sedimentation-rate (E.S.R.) (58 mm. in the first hour), nothing abnormal was found. Electrolytes were normal. We excluded Addison's disease.

She was again seen in 1957 when her complaints were the same; she was anæmic, with a high E.S.R. of 40 mm., and a low blood-pressure. Later she complained of symptoms suggestive of Raynaud's phenomenon. Lupus-erythematosus (L.E.) cells were absent. The globulin level was high, 4·6 g. per 100 ml., and γ-globulins 2·6 g. per 100 ml.

She was thought to have early scleroderma, and was treated with prednisolone, and improved. When seen again in 1960 her hæmoglobin level was 74%. E.S.R. was 54 mm. L.E. cells were present. She also had neutropenia and a raised γ-globulin level; treatment with corticosteroids was continued.

The skin was dry, the voice hoarse, the appearance waxy, the pulse slow, and flattened T waves were seen on the electrocardiogram. The blood-cholesterol level was 500 mg. per 100 ml., and an iodine-uptake determination confirmed the diagnosis of myxœdema.

I wish to thank Dr. R. E. Smith for his help and for permission to publish.

Gulson Hospital, Coventry, Warwickshire.

A. R. TAI.

NICKEL SENSITIVITY

SIR,—Dr. Stoddart's recent article [1] on local and generalised transfusion reactions caused by nickel-containing cannulæ prompts me to report a study which supports his observations. Among 621 patients with nickel dermatitis the possibility that injection needles were the cause was considered in 14. This could not be proved in 10, because the sites of injection on the thighs and in the elbow flexures coincided with the sites of predilection of primary or secondary nickel dermatitis,[2] and on the calves with the sites of predilection of varicose dermatitis. But in 4 cases, the relation between local nickel dermatitis and the use of injection needles was striking:

CASE 1.—A single shopgirl, aged 26, had had occupational nickel dermatitis of the hands for two years. A few hours after a diagnostic venepuncture circular vesicular dermatitis appeared distally in the right cubital fossa, around the site of injection, and the lesions gradually spread to her face, arms, and hands.

CASE 2.—A married woman of 21 had had twelve injections of an arsenic preparation ('Arsol') after childbirth. Dermatitis

Dermatitis caused by a nickel-plated syringe case.

appeared at the sites of injection on both hips, and spread to the upper arms, cubital fossæ, breasts, legs, and thighs, finally resulting in generalised prurigo. A patch test with arsol was negative, but with 5% nickel sulphate the result was strongly positive.

CASE 3.—A housekeeper, aged 45, had had nickel dermatitis caused by suspenders several years previously. After puncture of the right maxillary antrum she twice had œdema of the upper lip with irritation of its mucous-membrane lining, and dermatitis of the right part of her face and around the right eye. Each time the dermatitis followed four to five hours after the puncture and persisted for about two weeks. Neither local anæsthetics nor antibiotics were used, and the patient did not react to iodine which had been used as an antiseptic.

CASE 4.—A married woman of 28 had had dermatitis caused by suspenders six years previously; a patch test had been positive for nickel. When admitted to hospital for an abdominal operation she was given subcutaneous infusions of saline solution into both thighs. Dermatitis appeared at the sites of injection a few hours later, and lasted for four weeks. A year

5. Friou, G. *J. clin. Invest.* 1957, **36**, 890.
6. Friou, G. *Yale J. biol. Med.* 1958, **31**, 40.
7. Pollak, V. E., Mandema, E., Kark, R. M. *Lancet*, 1960, ii, 1061.
8. Roitt, I. M., Doniach, D., Wilson, E. G., Couchman, K. *Bull. Soc. Chim. Biol., Paris*, 1960, **42**, 1165.

1. Stoddart, J. C. *Lancet*, 1960, ii, 741.
2. Calnan, C. D. *Brit. J. Derm.* 1956, **68**, 229.

PATIENTS WITH NICKEL SENSITIVITY WHO HAD HAD COURSES OF SUBCUTANEOUS OR INTRAVENOUS INJECTIONS

Condition treated	No. of cases	Latent nickel sensitivity	Primary nickel dermatitis	Site of primary nickel dermatitis				Secondary nickel dermatitis
				Hands	Thighs	Calves	Generalised	
Diabetes ..	6	2	4	3	..	..	1	4
Syphilis ..	2	..	2	1	1	..	..	2
Varicose ulcer ..	13	9	(4)	..	..	(4)	..	(4)
Rosacea ..	4	4	..	..	..	..	..	..
Total ..	25	15	10	4	1	4	1	10

later she again got dermatitis after wearing nickel-plated suspenders.

11 of the 621 cases of nickel dermatitis were in nurses, doctors, and dentists, arising mainly from contact with surgical instruments. The figure shows circular dermatitis in the palm caused by the lid of a nickel-plated syringe case. This patient was a woman barrister, aged 31, who had had recurrent nickel dermatitis for six years, because from time to time she helped to give her mother insulin injections.

In the table are listed 25 patients from the series who had had injections for some time. A direct relationship can be seen between the length of the courses of injections and the spread of dermatitis, as well as an inverse relationship between the length of the course and latent nickel sensitivity. In the diabetics, however, dermatitis usually appeared first on the hands, apparently being caused by the syringes. In the 2 syphilitics the cause of the primary dermatitis was known, and we could not establish any correlation between spread and injection. All the diabetics were able to continue their own injections if they were careful in handling syringes.

The Finsen Institute,
Copenhagen, Denmark. POUL V. MARCUSSEN.

DIAGNOSIS OF ACUTE APPENDICITIS

SIR,—I was interested to read Mr. Bevan's shrewd points in diagnosing appendicitis (Feb. 18).

I have never sought two of the signs he mentions; but my experience fully accords with his statement that acute appendicitis is never present when cæcal gurgling is elicited on palpation of the right iliac fossa.

The mechanism of this phenomenon cannot readily be explained; and I see Mr. Bevan cleverly avoids this issue with a masterpiece of generalisation.

I have often found this sign in cases of enteritis: at times associated with hyperactive-bowel sounds, and in circumstances where the cæcum might well be expected to contain gas and fæcal fluid which would produce a gurgle on palpation. Yet under these conditions, but without gurgling, appendicitis can, and sometimes does, develop.

Again, the cæcum in these cases sounds as if it was a large organ—that is large per se and not due to distension. Usually such large, bulky cæcums are exposed when a normal "cold" appendix is being removed; but surely the size of the cæcum itself cannot safeguard against developing appendicitis?

It is, of course, quite understandable that the sign will be absent in the presence of multiple adhesions from previous attacks of appendicitis, or when there is a diffuse "plastic" inflammatory reaction involving all intraperitoneal structures in the right iliac fossa. However, I do not think that muscle guarding alone would cause the sign to disappear.

Undoubtedly this simple sign fully deserves a place in the diagnosis of the surgical abdomen. The mechanism of its production is clear, but its absence is not so readily understandable.

Stobhill General Hospital,
Glasgow. F. T. CROSSLING.

BRONCHITIS AND THE MINISTRY OF LABOUR

SIR,—Your annotation (Jan. 21) and the subsequent letter by Dr. Moore (Feb. 11), might suggest that, in this country, very little sheltered employment is provided for those with chronic bronchitis.

I do not think that it is sufficiently well known that Remploy was formed for the express purpose of employing all types of seriously disabled workers under suitable conditions of sheltered employment. There are now 90 factories in operation in England, Scotland, and Wales, employing altogether 6250 of the severely disabled.

All the disabled may have their names entered on the register of disabled persons at any employment exchange in the country. When employment at a Remploy factory is available, the disablement resettlement officer of the exchange concerned selects suitable candidates from his list of seriously disabled requiring sheltered employment, and submits their names for consideration to the Remploy works manager. Many with severe chronic bronchitis can thus obtain employment, who might otherwise be unable to do so. This is particularly true of areas such as South Wales (mining), and in many of the large industrial towns where chronic bronchitis is such a scourge.

These chronic bronchitics work side by side with the other disabled, because the policy of Remploy is to avoid segregating workers with different disabilities. Each factory has a part-time medical officer; and one of his duties is to see that the best possible conditions of employment are provided for the disabled employee. At the moment about 350 of those disabled by chronic bronchitis and emphysema are employed in Remploy factories.

I agree there are probably many other ways of tackling the problem, but I wish to draw your attention to the contribution Remploy is now making.

Remploy Ltd.,
Cricklewood,
London, N.W.2. W. E. MACLEAN
Principal Medical Officer.

REDUCTION OF ANTERIOR DISLOCATION OF SHOULDER WITHOUT ANÆSTHESIA

SIR,—I read Dr. Evans's article [1] with much interest. Dislocation of the shoulder is common; and without proper after-treatment recurrent or habitual dislocation may result. This is probably why so many Nigerians come to our hospital with recurrent shoulder dislocations—one, for example, dislocating for the ninth time after only simple movement. I have personal experience of this injury.

In December 1958, while skating on an ice-rink in London, I fell on my outstretched arm, and felt a sudden pain in my right shoulder; it was stiff, and I could not move my right arm. Shortly afterwards the shoulder muscles became spastic and very painful. To relieve the pain I kept my arm stretched and hanging; but the pain increased and I realised that I had dislocated my shoulder through the anterior capsule. In hospital this diagnosis was confirmed by X-ray. As I had to wait for some time I asked the house-surgeon for an injection of morphine, but was not given it; so I decided to relax the rotator-cuff muscles of the affected shoulder. I achieved this in the treatment room by letting the arm hang as Dr. Evans describes. By bending down and resting my body on the treatment table I could hang my arm over the side of it. After about 10 minutes the pain had completely disappeared; when the house-surgeon came to reduce the dislocation, the shoulder was painless and I could even move it a little. I asked him to reduce it without anæsthesia; and he used Kocher's method as described in Christopher's *Textbook of Surgery*.[2] At the second attempt it snapped back into place. The most remarkable thing about the procedure was its painlessness. Only at the moment when it snapped back did I feel some discomfort.

1. Evans, D. K. *Lancet*, 1960, ii, 1419.
2. Christopher's Textbook of Surgery (edited by L. Davis.) London, 1956.

If the patient feels uncomfortable in the prone position, I would suggest placing him carefully on his back. I consider that the greatest advantage of the technique Dr. Evans describes is the relaxation of the cuff muscles. If this has been achieved even the ordinary Kocher's method without anæsthesia is fully justified. The supine position has an advantage over the prone as in the former the surgeon is not hindered in his manœuvres.

Here anterior dislocations are most common and reduction is usually simple. But much depends upon the intelligence and understanding of the patient; often he is unable to relax—the most important prerequisite for reduction.

Cooperation cannot always be expected from a patient who finds it hard to understand the underlying principle. That is why we often have to do reductions under general anæsthesia. With more enlightened patients in Europe it might be worth trying my suggested method.

Mkar Christian Hospital,
via Makurdi, Nigeria. L. VAN IEPEREN.

UNSTERILISED HYPODERMIC NEEDLES

SIR,—We should like to draw attention to recent practices in the marketing of hypodermic needles. These are now being sealed in aluminium and plastic foil. Each needle is individually wrapped and a continuous " belt " of a dozen needles is enclosed in an outer cardboard carton. Some of the needles have been sterilised and the outer carton is labelled " Sterilised for immediate use ". Others, presumably unsterilised, are issued in cartons bearing no reference to sterilisation. No wording or other sign appears on the individual foil wrapping which is the same in both cases, and moreover the two kinds of needle appear identical except for the hub (which is plastic in those claimed to be sterilised). Therefore after the needles have been removed from the outer carton there is nothing to show which have been sterilised and which have not. It is obviously inadequate to rely on the presence of a plastic hub to indicate sterility.

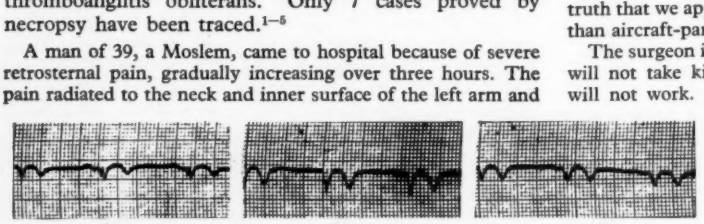
Each individual needle should be unequivocally marked. Meanwhile hospitals would do well to examine their existing stocks.

Lewisham Hospital,
London, S.E.13. MARY MCMILLAN
J. PIRNIE.

MYOCARDIAL INFARCTION DUE TO THROMBOANGIITIS OBLITERANS

SIR,—Coronary disease is rarely associated with thromboangiitis obliterans. Only 7 cases proved by necropsy have been traced.[1–5]

A man of 39, a Moslem, came to hospital because of severe retrosternal pain, gradually increasing over three hours. The pain radiated to the neck and inner surface of the left arm and forearm, and was associated with excessive sweating, nausea, and some vomiting. He had five years' history of thromboangiitis obliterans, with intermittent claudication of both legs; and a year ago the terminal phalanx of the third left toe had been amputated. A left lumbar sympathectomy had been performed five months ago.



Electrocardiogram taken on admission.

The pulse was 100 per min. and blood-pressure 110/70 mm. Hg, and he was pale and sweating. The pulses were absent in both limbs in the dorsalis pedis and posterior tibial arteries, and the wound of the amputated toe was still open, but the left leg (side of the sympathectomy) was warmer than the right. A myocardial infarction was diagnosed and he was given morphine and an anticoagulant. An electrocardiogram showed a fresh posterior infarction. The patient recovered but he now has angina and is, of course, further restricted by the obliterative condition of the leg vessels.

Faculty of Medicine,
University of Alexandria. M. ESSAM FIKRY.

SURGEON AND ENGINEER

SIR,—Orthopædic surgeons often appear mystified when their plates or screws sometimes break and sometimes do not, or when one plated fracture does well and another badly. But they rarely concern themselves with the design of internal splintage, so wide is the gulf between surgery and engineering.

No specification has ever been published for any plate in common use—with one exception, and even for this manufacture does not closely follow the specification. When a surgeon orders a Venable plate it is the manufacturer who decides the thickness and, using no more than his common sense, cuts off a piece of 10-gauge strip for the longer plates and 12-gauge for the shorter. Moreover, if the surgeon wants an unusually large screw, the manufacturer will obligingly drill large holes, despite their weakening effect. But many surgeons would be suspicious of any form of control that might limit their freedom to order as they wish. Furthermore, it would be impossible to get them to agree among themselves on whether they want high or low rigidity. These are only two of the difficulties to be overcome in solving the problem posed in your annotation (Feb. 11).

As for the fiasco with the acrylic Judet prosthesis mentioned by Mr. Zarek (March 11), all the information was available almost from the start to show that it would fail mechanically. A certificate from the National Physical Laboratory showed that the appliance would stand up to body-weight—and added that when tested to destruction three times body-weight was required. An anatomical paper published a few years previously had shown that the pull in one of the hip muscles in quiet walking is nearly twice body-weight. From this it was very simply deduced that the pressure on the head of the femur would be nearly three times body-weight. It was not by accident therefore that the Judet prosthesis broke—it was a scientific certainty. Reading between the lines it seems likely that because of ignorance of anatomical mechanics the N.P.L. was asked the wrong question. It has been said with much truth that we apply far less skill to designing surgical metalware than aircraft-parts.

The surgeon is not very amenable to scientific discipline. He will not take kindly to being told that some cherished idea will not work. He is much more inclined to ignore theory and " try it out ", as though patients were expendable experimental material. Yet before he can cooperate with the engineer he must recognise the absoluteness of science properly applied. Having long familiarity with misapplied science (as in the example above), and having been let down by incorrect conclusions in the past, he quite justifiably loses his trust and is apt to declare that surgery is an art and not a science. I have even heard a reputable orthopædic surgeon declare that he was not convinced that the human body always obeyed the laws of physics.

Whilst agreeing that improvement is necessary—at least in this branch of surgical engineering—the difficulties to be overcome will be, therefore, apathy and a little antagonism on the part of the surgeons—the former

1. Hausner, E. Thesis, Postgraduate school, University of Minnesota, 1939.
2. Hausner, E., Allen, E. V. *Ann. intern. Med.* 1938, **12**, 845.
3. Freidberg, C. K. Diseases of the Heart; p. 442. Philadelphia, 1956.
4. Richard, R. C. *Brit. med. J.* 1953, **i**, 478.
5. Allen, E. V., Barker, N. W., Hines, E. A., Jr. Peripheral Vascular Diseases; p. 295. Philadelphia, 1955.

because there is so much ignorance of mechanics that many cannot even comprehend the need for more knowledge; and the latter arising from the jealous guarding of his right to design and order any appliance he thinks fit. Whatever organisation is finally evolved must achieve its ends not by compulsion, but by teaching, example, and an output of unmistakably good work.

Birmingham Accident Hospital,
Birmingham, 15. J. H. HICKS.

SMOKE AND LUNG CANCER

SIR,—Your leading article of Feb. 4 left the impression that air pollution is an important factor in the ætiology of lung cancer. I would have thought it desirable, in a matter of such public interest, that reference should be made to the work of more than one individual in this field. For instance, results [1] from a detailed comparison of the 83 county boroughs in England and Wales showed a high correlation between air pollution and bronchitis mortality, and a relatively low correlation between air pollution and lung-cancer mortality. It also showed that the size of a town, independently of air pollution, was related to lung-cancer mortality; a point worth making, surely, when drawing conclusions from data relating to population densities.

Ulverston,
Lancs. CHARLES DALY.

SEX-DETERMINATION IN MAN AND IN DIPTERA

SIR,—The Y chromosome seems to act as a dominant male-determinant in mammals.

The karyotype XO is phenotypically a female (Turner) in man, and a fertile female in mice. The karyotype XXY is a male in mice and a male (Klinefelter) in man. Two cases of Klinefelter syndrome with the karyotype XXXY have been reported, which demonstrate that the Y chromosome is dominant even to 3 X chromosomes. At first the interpretation of such discoveries was difficult by comparison with the sex-determination in drosophila, in which XO is a male and XXY a fertile female. In the latter case the sex is determined solely by the relative number of X chromosomes. It is noteworthy that an entirely new type of sex-determination has now been discovered in another fly, the Phorid *Megaselia scalaris*. Here the male sex is determined by a dominant factor, located at the top of a chromosome. This locus can change its position by translocation between all the non-homologous chromosomes. In accordance with the position of the sex-determinant either one or the other linkage-group behaves as partially sex-linked. This mechanism of sex-determination is incompatible with a partially inert Y chromosome and with sex-linked inheritance; and it certainly is not found in mammals. The *tertium comparationis* is the dominant action of a male-determinant, here also present in a species of Diptera.

Institute of General Biology,
University of Vienna. F. MAINX.

NOMENCLATURE IN GENETICS

SIR,—Since the recent demonstration that mongolism is associated with trisomy of chromosome no. 21,[2] reports have appeared relating specific clinical syndromes to various chromosomal aberrations in man. Although little is known about the viability of the more severe karyotype derangements, it is clear from elementary algebraic considerations that the number of possible chromosomal aberrations in man is astronomical. There are over 4,000,000 theoretical possibilities for the trisomic state alone.[3] Possible combinations of trisomy and monosomy in the same individual total more than 31,000,000,000.

To designate each of these clearly and simply, a standard system of nomenclature seems necessary. A system analogous to chemical nomenclature may perhaps be the simplest. For example, an individual trisomic for chromosomes nos. 12 and 17, monosomic for no. 22, and with an XXY sex-chromosome constitution, might be designated as:

12, 17-triplo-22-mono-XXY

Abnormalities of portions of chromosomes (duplications, deletions, inversions, and translocations) present more difficulties. Perhaps readers of this journal may suggest a workable terminology to cover all possibilities.

Department of Pediatrics,
George F. Geisinger
Memorial Hospital,
The Foss Clinic,
Danville, Pennsylvania. JOHN C. GALL, Jr.

MEDIEVAL FAMINES AND 20th-CENTURY HEART-DISEASE

SIR,—When preparing a lecture recently I was struck by the number and severity of the famines in the Middle Ages, especially in the first half of the 14th century.

These followed a secular change in the weather which had begun in the middle of the last decade of the previous century and lasted until the mid-forties of the 14th century. The climatic changes led to a series of crop failures and poor harvests, often in successive years. Contemporary accounts tell us of cannibalism in isolated villages, where parents consumed their dead children; and Holinshed [1] informs us that newly incarcerated prisoners were torn to bits and eaten by their famished fellow gaol-inmates. The Black Death struck towards the end of this period, adding to the misery of the population, and to make matters worse, at least so far as Western Europe was concerned, the Hundred Years War began, bringing more disease, misery, and famine in its train. These disasters had reduced the population of England by at least a third by the end of the century; but the material and human losses suffered by France by the time the struggle between the two countries ended were even greater and equalled those in World War II.

Famine seems to have been an everpresent hazard to most human communities, in prehistoric and historic times almost till the present century. The great famine after the potato blight just over a century ago in Ireland reminds us how near in time we are, even in these islands, to this important demographic hazard. Although actual famine did not feature in the Industrial Revolution, inadequate nutrition was quite common, as is evidenced by the small stature and delayed puberty of most of the town-dwellers of these islands during the last 150 years or so: a situation which has been remedied as a result of the 2 world wars, so that the population is now adequately fed with good-quality protein and vitamins, but may well be over-supplied with calories.

Those members of a population who can store up food for times of scarcity may well be at an advantage for survival from the genetic point of view; and fat is the most convenient depot. Most adults in the more advanced countries have a two months' reserve of fat, while the obese may have sufficient to survive for eight or more months on very short rations. Without going into details of the number and mode of action of these genes, let us call them the "food-storing" genes. Famine will tend to spare those with such genes; but when food is plentiful, especially if permanently so, then these genes no longer confer biological advantages, and may even be disadvantageous. If this is so, we may well be paying the price for the survival of our ancestors during the many centuries when famine prevailed; and we should expect this price to be exacted first in those populations producing surplus food and consuming excess calories. These conditions were fulfilled for the first time on a large scale in this century in the United States, and have now become a feature of the diet of the more advanced countries, coincident with increased coronary disease.

1. *Brit. J. prev. Soc. Med.* 1959, **13**, 27.
2. Lejeune, J., Gautier, M., Turpin, R. *C.R. Acad. Sci., Paris*, 1959, **248**, 602.
3. *Bull. Geisinger Memorial Hospital and Foss Clinic*, 1960, **12**, 115.

1. Holinshed, R. Chronicles of England, Scotland, and Ireland. London, 1578.

Fasting and the consumption of fish in medieval times may well have considerable bearing on the present-day problem of coronary disease, if the fats consumed in the diet are really concerned in its ætiology. Neither should we forget that there was no compulsion " to keep up with the Joneses " in a society which had a fixed place for virtually every individual, ordained by a divine providence; and this possibly benefited his cardiovascular system.

Famine still hangs as a threat over the heads of millions in Asia, Africa, and South America; and it has been a selective factor in human populations since the earliest palæolithic hunter pursued his quarry on the fringes of the retreating ice-caps. May not the steatopygia of the Hottentot Venus figurines represent the desire for a very necessary food-storing capability rather than a fertility symbol? If the increase in world population is not halted it may threaten us all, with results which future historians will no doubt find interesting and puzzling.

Careful studies of the dietary habits of peoples in the past should throw considerable light on some contemporary problems and may serve as a useful check on the more exuberant hypotheses of the ætiology of modern maladies. Genetics can sometimes help the historian; if we took more interest in the history of medicine, we too could help the geneticists, and in doing so help ourselves to understand ourselves.

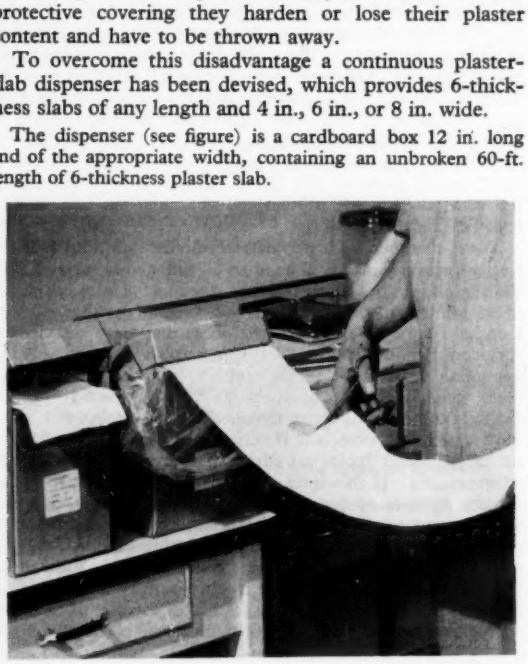
Guy's Hospital,
London, S.E.1. E. J. MOYNAHAN.

A CONTINUOUS PLASTER-SLAB DISPENSER

SIR,—Manufactured plaster slabs are not as popular as the proprietary rolled plaster bandage. Slabs are still usually made by unrolling the requisite amount of a bandage of suitable width. Presumably one of the advantages justifying the extra time involved is that a slab of the exact size needed can be prepared. Manufactured slabs are available in only two lengths (15 and 30 in.); and these only rarely fit the requirements exactly. If too short, nothing can be done; if too long they can be shortened, but only with considerable wastage. Off-cuts are rarely used: they accumulate, and without their protective covering they harden or lose their plaster content and have to be thrown away.

To overcome this disadvantage a continuous plaster-slab dispenser has been devised, which provides 6-thickness slabs of any length and 4 in., 6 in., or 8 in. wide.

The dispenser (see figure) is a cardboard box 12 in. long and of the appropriate width, containing an unbroken 60-ft. length of 6-thickness plaster slab.



The non-detachable lid is hinged towards one end to form a trap-door through which the slab is withdrawn. In use, the end can be left projecting; otherwise the box is kept shut and damage to the slab is prevented.

These slabs have proved extremely satisfactory. With care in measurement there is no wastage. Much time is saved by making the plaster cast mainly of slabs with a minimum number of rolled bandages. A below-knee plaster, for instance, can be applied in 3 minutes using two slabs and two 6-in. bandages.

They can also be used in a figure of eight to reinforce a plaster jacket or a hip spica. Application is quicker and the cast can be lighter.

These slabs should be valuable in forward medical aid units where the use of encircling plaster bandages for first-aid techniques is inadvisable.

My thanks are due to Mr. P. S. Watson, and the staff of Messrs. Smith & Nephew, Ltd., for their help and collaboration in developing the slabs and containers.

Whiston Hospital,
Prescot,
Lancashire. M. H. HALL.

BILLIARDS CRAMP

SIR,—A man of 61 complained that he could not play billiards because " his arm went out of action ".

He explained that he had no difficulty in taking up position to play a shot, but when he drew his elbow back preparatory to striking the ball, the arm seemed to seize up, and he could not move it. He could move the cue backwards and forwards while preparing to strike: it was the actual return of the cue to the ball that was interrupted.

No other physical activity was affected. He felt perfectly well, and had never been seriously ill. There were no physical signs on examination.

He had been an administrative executive in a public authority and had retired a year ago to look after his 92-year-old mother. He was unmarried, and had always lived with his mother. The billiards symptom came on soon after he retired. This seems to be akin to so-called " writer's cramp ", with muscles refusing to carry out a clearly defined action. As in writer's cramp, there seemed to be a background guilt complex.

I explained to him that he could be sent for psychiatric investigation and treatment, but advised that as he was perfectly happy and did not need to play billiards, he should do nothing, as the power to play might possibly return as unaccountably as it failed.

London, W.1. P. F. ASHTON.

ORAL PROGESTOGENS

SIR,—Treatment of habitual abortion with progesterone is regarded with suspicion because of conflicting results after indiscriminate use of the hormone. Dr. Osmond-Clarke and Dr. Murray (March 11) state quite rightly that patients should be selected for treatment on the basis of deficient progesterone in the pregnancy under observation, and not merely on the history. They assessed progesterone deficiency by vaginal smears, and other investigators assayed pregnanediol excretion.

A simple method of selecting patients suitable for progesterone therapy has been described by Macdonald and Sharman [1] using cervical-mucus smears. 2 or more unstained dried smears showing salt crystals or " ferning " under the low-power microscope indicate an œstrogen-progesterone imbalance which carries an approximately 50% risk of abortion in any patient—probably much higher where the history is bad. These patients respond extremely well to progesterone therapy, and prolonged trial along these lines should prove the real value of progesterone. Conversely, unless the fœtus is abnormal, the absence of crystals carries a good prognosis without any treatment. At the moment we are using weekly injections of 250 mg. 17α-hydroxyprogesterone caproate but the test could be used in any trial, and for other materials.

1. Macdonald, R. R., Sharman, A. *Int. J. Fertil.* 1959, **4**, 338.

This method of selection is suitable for general use, since the test and the interpretation of the findings are both very easy.

Department of Obstetrics and Gynæcology, University of Leeds. R. R. MACDONALD.

GENERAL PRACTICE

SIR,—May I suggest a very obvious reform which is not mentioned by Dr. Evans and his colleagues in their article last week.

The Royal Commission recommended an average increase for general practitioners of 22·8% over the 1955–56 figures, which in fact were the same as the 1952–53 figures.

When the Central Pool was finally allocated, it was found that the vociferous minority had secured large increases for themselves, leaving a full-time general practitioner with a list of 3000 only approximately 15% better off than he was in 1952–53.

The inference is that it is unwise to work full-time as a general practitioner in the N.H.S.

My suggested reform would be to stop the allocation from the Central Pool of grossly disproportionate payments: for example a general practitioner on the maternity list, who has 100 midwifery cases a year on his books, is paid the same per year as a general practitioner not doing midwifery with a list of 3000, though he looks after only 1260 patients.

London, S.E.5. B. H. O'NEILL.

SIR,—There are some who believe that the capitation system is really a salaried service, in which payment is based largely upon geography, rather than seniority.

In their article, Dr. Evans and his colleagues state that the Royal Commission was told of no satisfactory alternatives to the capitation system of payment.

Paragraph 75 of the minority report, to which they refer, contains nothing to support this contention. It actually says: "It is disappointing that none of the evidence placed before us, and none of the ideas discussed within the Commission itself, have produced any promising means for placing a direct premium on quality of work . . . "

It should be pointed out that a discussion about a direct premium on quality of work is not the same as a discussion about alternative methods of remuneration. The former could be compatible with capitation payment, the latter is not. This paragraph continues, " . . . one line of investigation which might be fruitful is whether increasing weight could be given to item of service ". It is surprising to find this quoted in support of the capitation principle.

Although much relevant evidence was taken by the Commission, none was given on alternative methods of remuneration, as this subject was outside the terms of reference. This, however, did not prevent it from recommending an entirely new method of payment for general practitioners—namely, merit awards.

Worthing, Sussex. R. H. DAVISON.

TRIPARANOL IN XANTHOMATOSIS

SIR,—3 cases of xanthomatosis attend Dr. C. J. Fuller's clinic at this hospital. They have been treated with nicotinic acid in doses of up to 2 g. daily in combination with various amounts of maize oil. All have progressed favourably as judged by disappearance of the skin lesions and reduction of serum-cholesterol levels.

They complained of the unpleasant side-effects of nicotinic acid, and for this reason it was decided to try the new compound triparanol ('Mer-29').[1] This is supposed to lower serum-cholesterol by impairing cholesterol synthesis in the liver.

The nicotinic acid and maize oil were discontinued, and triparanol was given in doses of 250 mg. daily. In all cases the serum-cholesterol level rose strikingly.

Age (yr.)	*Sex*	*Before treatment*	*Nicotinic acid and maize oil*	*Triparanol*
46	M	513 (1)	333 (7)	437 (2)
61	F	487 (1)	299 (8)	580 (2)
54	F	564 (1)	415 (5)	670 (5)

Figures in parentheses indicate number of observations.

Electrophoretic lipoprotein analysis confirmed an increase in the α-, β-, and ω-lipoprotein fractions.

Serum-cholesterol levels are known to fluctuate widely, but it seems reasonable to conclude that in doses of this amount triparanol is ineffective in lowering the serum-cholesterol in xanthomatosis, and cannot replace nicotinic acid and maize oil for this purpose.

Royal Devon & Exeter Hospital, Exeter, Devon. G. H. HALL.

1. See *Lancet*, 1960, ii, 968.

SERUM-LIPOPROTEIN LEVELS IN NIEMANN-PICK DISEASE

SIR,—Recently an 11-month-old Caucasian boy was admitted to our hospital suffering from generalised malnutrition and abdominal enlargement. Microscopical examination of bone-marrow aspirate revealed features consistent with Niemann-Pick disease. Histological study of tissue obtained at necropsy some 5 months later disclosed the presence of Niemann-Pick cells in liver, spleen, lungs, thymus, lymph-nodes, and bone-marrow. Quantitative partition of phospholipids was performed on an aliquot of hepatic tissue according to the method of Schmidt and coworkers.[1] The total phospholipid phosphorus amounted to 5·1 mg. per g. wet weight, of which 3·3 mg. per g. was accounted for as sphingomyelin. Thus approximately 65% of the liver phospholipid was sphingomyelin, whereas normally this fraction ranges from 5 to 10% of the total.

A review of the history revealed that at 2 months the child exhibited a moderately elevated serum-total-cholesterol value of 242 mg. per 100 ml. Pick [2] has suggested that hypercholesteræmia is usually associated with the Niemann-Pick syndrome; other workers [3 4] have not confirmed this. Of 13 Niemann-Pick patients recently presented by Crocker and Farber,[5] 6 had a raised serum-total-cholesterol. Until now serum-lipoprotein levels had not been extensively studied in the Niemann-Pick syndrome. Therefore during the 4-month period before the death of the child serum total, α-, and β-lipoprotein cholesterol measurements were made repeatedly according to a technique described elsewhere.[6] At the time-intervals studied serum-total-lipoprotein-cholesterol levels were consistently elevated. Furthermore the serum-cholesterol appeared to be abnormally distributed between the two

Date	*Lipoprotein-cholesterol* α-*fraction* (*mg. per 100 ml.*)	β-*fraction* (*mg. per 100 ml.*)	*Total* (*mg. per 100 ml.*)	β : α
Nov. 21, 1960	30	272	302	9·1
Nov. 25	30	282	312	9·4
Dec. 2	22	254	276	8·7
Dec. 6	30	302	332	9·9
Dec. 9	24	306	330	10·2
Dec. 22	30	280	310	9·3
Jan. 6, 1961	30	243	273	8·1

lipoprotein fractions. Nearly 90% of the cholesterol was found in the β-fraction. In contrast, clinically healthy newborns as well as older infants have appreciable amounts of lipid material associated with both α- and β-lipoproteins. For example Barr [7] reports that α-lipoproteins of cord-blood contain on the average 43% of the serum-total-cholesterol. Angelopoulos and

1. Schmidt, G., Benotti, J., Hershman, B., Thannhauser, S. J. *J. biol. Chem.* 1946, **166**, 505.
2. Pick, L. *Amer. J. med. Sci.* 1933, **185**, 453, 601.
3. Sperry, W. *J. Mt Sinai Hosp.* 1942, **9**, 799.
4. Thannhauser, S. J. Lipidoses, Diseases of the Intracellular Lipid Metabolism. New York, 1958.
5. Crocker, A. C., Farber, S. *Medicine*, 1958, **37**, 1.
6. Searcy, R., Bergquist, L., Jung, R., Craig, R., Korotzer, J. *Clin. Chem.* 1960, **6**, 585.
7. Barr, D. *Circulation*, 1953, **8**, 641.

Bechrakis [8] studied Oil-Red-O-stained electrophoretic patterns obtained from sera of 12 apparently normal 1- to 3-year-old infants. These workers observed that nearly 30% of the lipophilic dye was taken up by α-lipoproteins. In our case of Niemann-Pick disease the β- to α-lipoprotein-cholesterol ratio was persistently elevated, ranging from 8·1 to 10·2.

The total low-density lipoprotein spectrum of S_f 0–400 was also estimated on several occasions by an immuno-chemical technique recently introduced by Heiskell and coworkers.[9] The column of precipitate produced by mixing serum with a specific β-lipoprotein antiserum (sold by Hyland Laboratories, Los Angeles, California) was measured in a standardised capillary tube. We have observed in our laboratories with this procedure that sera from normal infants or adults rarely produce more than 1·0 and 2·0 mm. of precipitate respectively. On the other hand values of 4·0 and 4·5 mm. of precipitate were obtained when the child we studied was 13 and 14 months old. Shortly before death at the age of 16 months the amount of lipoprotein precipitate measured only 2·8 mm.

These data suggest that low-density lipoproteins rich in triglyceride, as well as the higher density β-fractions containing large quantities of cholesterol, were elevated. It is noteworthy that none of the serum samples from the child exhibited detectable lipæmia. Thannhauser [4] points out that in most cases of Niemann-Pick disease hyperlipæmia is not present.

This investigation was supported in part by grants from the American Osteopathic Association, the U.S. Public Health Service, Baxter Laboratories, and the Attending Staff Association of the Los Angeles County Osteopathic Hospital.

Los Angeles County Osteopathic Hospital, College of Osteopathic Physicians and Surgeons, Los Angeles, California.

RONALD L. SEARCY
VINCENT P. CARROLL, JR.
LOIS M. BERGQUIST.

SYMPATHOLYTIC DRUGS AND THE DOPA AWAKENING EFFECT

SIR,—Carlsson et al.[10] and Everett and Toman [11] found that L-DOPA (β-3:4-dihydroxy-L-phenylalanine) in large doses produced an awakening effect in reserpine-treated mice and monkeys. Blaschko and Chruściel [12] confirmed this result and tested certain other aminoacids related to phenylalanine for their awakening effect. Only metatyrosine (*m*-hydroxy-DL-phenylalanine) showed a similar awakening effect in reserpinised and reserpine- and iproniazid-treated mice. More recently we have noted in our laboratory that L-DOPA in doses of 250–1000 mg. per kg. produces an awakening effect in white rats of the Wistar strain and in guineapigs treated with reserpine (15 mg. per kg.) and iproniazid (100 mg. per kg.). The awakening effect is followed by a period of overactivity which lasts approximately 30 minutes in guineapigs and 2 hours in rats.

When white mice of strain A, treated with reserpine (3 mg. per kg.) 16 hours before injection of L-DOPA (1000 mg. per kg.), and with iproniazid (100 mg. per kg.) 2 hours before the L-DOPA injection, were given sympatholytic drugs, the DOPA-awakening effect underwent a remarkable change. Mice treated with phenoxybenzamine (' Dibenyline ') (5–20 mg. per kg.) 5–16 hours before L-DOPA did not show the DOPA-awakening effect. Mice treated with guanethidine (' Ismelin ') in a dose of 30 mg. per kg. 2 hours before L-DOPA were more active and overexcited compared with those not given guanethidine. The increase of DOPA-awakening effect by guanethidine was evident. But bretylium tosylate (' Darenthin ') (20–40 mg. per kg.) injected 16 hours before L-DOPA did not increase the DOPA-awakening effect.

Manometric assay of mouse-liver decarboxylase activity, performed as described previously,[3] has shown phenoxybenzamine to be a slow-acting inhibitor of decarboxylase, whereas bretylium tosylate and guanethidine have no effect upon this enzyme. Manometric measurement of amine-oxidase activity of dog serum revealed that guanethidine inhibits this enzyme in concentrations between $10^{-3}M$ and $10^{-5}M$.

These results seem to support the view that DOPA-awakening effect is caused by dopamine formed in some " strategic positions " in the midbrain.[3] The inhibition of decarboxylase prevents the formation of dopamine, and the inhibition of amine oxidase arrests the enzyme which causes a rapid deterioration of the biologically active catecholamine.

Further experiments are in progress, and details will be published elsewhere shortly.

Department of Pharmacology, Silesian School of Medicine, Zabrze, Poland.

T. L. CHRUŚCIEL.

FROZEN BLOOD FOR TRANSFUSION

SIR,—Your comments [1] were read with interest here, since the process referred to was developed in these laboratories. But we wish to point out one questionable conclusion.

You state that the principal contraindication to the use of this method is its cost. It should be noted that the " rough costing " figure of about £6 per unit was based on a research project in which no effort was made to control the expense. The equipment was an elaborate research apparatus designed for a totally different purpose from red-cell processing. Now that the method has proved important in therapy, mechanical simplification of the equipment is in progress. This aims to develop a disposable plastic bowl in which the entire process of blood collection, centrifugation, glycerolisation, storage at −70°C, deglycerolisation, resuspension in the original plasma, and administration to the patient can be effected.

As you correctly point out, the research model of the Cohn fractionator is already efficient and inexpensive enough to justify its use for establishing a bank of rare blood-types and for other special purposes—autologous blood-banks, and " tailored " red cells resuspended in media modified for specific conditions (e.g., uræmia, burns, and hyperkalæmia).

Blood Characterization and Preservation Laboratory, Protein Foundation, Inc., Jamaica Plain, Massachusetts.

JAMES L. TULLIS.

MEDICINE AND AGRICULTURE

SIR,—Two years ago, farming became one of my major interests and I have been impressed by the wide range of experiences relevant to human physiology and medicine.

Briefly, I would refer to sexual physiology, surgical and hormone castration, toxæmias of pregnancy, abortions, sterility, lactation, mastitis, intestinal parasites, anæmias, antibiotics in infections and for growth, the apparent influence of sexual maturity on warts and ringworm, actinomycosis, control of tuberculosis and virus diseases, virus vaccines, calcium and magnesium deficiency syndromes, balanced feeding, and food conversion rates.

Another important angle, allied to my primary interest of endocrinology, is the fundamental studies in Australia on adrenal corticosteroid secretion in the conscious sheep, using autotransplanted adrenal glands.[2 3]

These reflections on the relationship between medical and agricultural experiences suggest that all medical students might spend weekends, holidays, or organised periods of some months, on farms. They could prove of help to the farmer in appro-

8. Angelopoulos, B., Bechrakis, G. *J. Pediat.* 1960, **57**, 66.
9. Heiskell, C., Fisk, R., Florsheim, W., Yachi, A., Goodman, J., Carpenter, C. *Amer. J. clin. Path.* (in the press).
10. Carlsson, A., Lindqvist, M., Magnusson, T. *Nature, Lond.* 1957, **180**, 1200.
11. Everett, G. M., Toman, J. E. P. *in* Biological Psychiatry (edited by J. H. Masserman); p. 75. New York, 1959.
12. Blaschko, H., Chruściel, T. L. *J. Physiol.* 1960, **151**, 272.

1. *Lancet*, 1960, ii, 1018.
2. McDonald, I. R., Reich, M. *J. Physiol.* 1959, **147**, 33.
3. Reich, M., McDonald, I. R. *J. Endocrin.* 1961, **21**, 387.

priate periods and would, at the same time, learn a great deal in an interesting way. Of course, individuals already do so here and there, but I am suggesting deliberations that might lead to a more systematic and widely spread interest and achievement.

London, W.1. S. LEONARD SIMPSON.

SEX AND PSYCHIATRY

SIR,—Dr. Oliver (March 18) rightly criticises the system in some psychiatric hospitals whereby consultants treat male or female patients only, but it is hard to see why he calls it "unscientific". Are pædiatrics and gynæcology the less scientific for treating children or women exclusively? One might, indeed, argue that specialisation in the mental disorders peculiar to each sex permitted the greater scientific benefit.

Division into male and female blocks is an archaic administrative convenience, and objections to it are ethical and practical—that a consultant admitting from outpatients may lose the case. The position may become worse when transfer from acute to convalescent or chronic wards entails further disturbing changes of physicians. The "firm" system whereby each consultant controls beds of each sex and category is the answer, and this system is spreading. But when consultants have to share wards, it may not be as easily arranged as in general hospitals: psychiatric treatment involves careful administrative decisions on nursing techniques, locked doors, and ward activities of all kinds throughout the 24 hours. The "responsible medical officer" will always be responsible for much more than the choice of tranquilliser and date of discharge; and consultants' views on therapeutic community developments do not always coincide. (It is coordination of the "global" approach to mental treatment that points so clearly to the need for a medical superintendent of some kind.) However, one can well imagine that sometimes closer harmony and better results may be obtained where one doctor looks after a whole ward—even at the expense of a one-sexed horizon. Many wards are now being opened to both sexes, and this helps in several ways.

Psychiatric administration has made contributions of its own, however archaic some places may still be. The whole concept of group methods, pioneered at the Henderson Hospital and elsewhere, is finding an increasing place in nursing, teaching, and organisation generally; and day hospitals are spreading from psychiatric to social and physical spheres. It is my opinion that some of our most advanced mental hospitals are administratively well ahead of anything in general medicine.

Dr. Oliver's other vaguer accusations of unscientific behaviour need to be amplified. Though closer integration with general medicine is well worth pressing for (it is inherent in the 1959 Act), it might be argued who is going to learn most from whom. Psychiatrists have long been aware of the need to validate their findings and have surely tested, double-blinded, more remedies in recent years than any other discipline; the social and community side of the work, too, is under intensive scrutiny. In medicine itself, such "scientific" things as physical signs, X-rays, and electrocardiograms are now known to be subject to large observer-error; and placebo-effect must be taken into account with the most organic of symptoms such as angina of effort. Surgery, of course, remains terra incognita—largely uncharted by double-blind techniques or placebo studies of any kind.

Will Dr. Oliver make it clearer what psychiatry has to learn from general medicine, and what are the "unscientific" sins which beset it?

Beckenham, Kent. RICHARD FOX.

SIR,—The anachronism of mental hospitals being divided into male and female sides, so rightly called an anachronism by Dr. Oliver, has been abolished here. May I assure Dr. Oliver that all the consultants in this hospital treat both male and female patients; and every consultant has acute and long-stay male and female beds.

The Towers Hospital, Humberstone, Leicester. H. B. KIDD.

TOXIC CHEMICALS ON THE FARM

SIR,—Some of the comments on the recent report issued by the Royal Society for the Protection of Birds on deaths of birds and animals connected with toxic chemicals have, indeed, as you say in your annotation of March 18, been expressed in exaggerated language, but you do not help the matter by leaning heavily on another report by Sir William Slater which is, admittedly,[1] based on evidence obtained six years ago.

The position, surely, is that no inconsiderable numbers of birds and mammals have been found dead, poisoned by these chemicals. By the end of this year it may be possible accurately to assess the extent of the damage. But almost nothing is known about the cryptic side-effects of these chemicals on the microflora and fauna of the soil, and neither the Ministry nor the Association of British Manufacturers of Agricultural Chemicals are prepared to say when challenged in the Press[2] what research is going on into any of these problems.

Savage Club, London, S.W.1. JOHN HILLABY.

SAFETY OF IRON PREPARATIONS

SIR,—Mr. D'Arcy and Miss Howard (Dec. 10) have conducted some very interesting and enlightening experiments in dogs to show the tremendous variation in toxicity of various salts of iron. On the results of their experiments, they conclude that ferrous carbonate is 100 times safer than ferrous sulphate. They therefore suggest that the carbonate should be used in preference to other salts of iron to help to reduce the number of children who die accidentally after taking large doses of iron.

I have not had the opportunity of observing the effects in humans of a gross overdosage of ferrous carbonate such as they gave in their experiments, but I was recently thankful that I had prescribed ferrous carbonate ('Ferrodic' tables) instead of some other, more toxic, form of iron.

A two-year-old child ate 15 of his mother's ferrodic tablets; the total amount of ferrous iron ingested was 750 mg. A salt and water emetic was immediately administered by the mother, and shortly afterwards repeated. Vomiting and diarrhœa ensued and the next day the child was quite well again.

Harthill, Lanarkshire. S. H. P. MCLAUCHLAN.

PLATELET-SUSPENSION SUBSTITUTE FOR THROMBOPLASTIN-GENERATION TEST

SIR,—Routine clinicopathological investigation of patients with a history of repeated minor hæmorrhagic episodes is usually unrewarding. Thromboplastin generation is probably the best further investigation; but there are so many of these cases that it is not practicable in all because of the work involved in preparing a platelet suspension[3] or a phospholipid emulsion.[4]

We have found a fraction of soya-bean phospholipid, 'Essential' (prepared by Natterman, Cologne), sold in this country as capsules of 'Lipostabil' (Aspro-Nicholas Ltd., Slough, Bucks), a satisfactory and stable alternative.

A single capsule is fragmented in 25 ml. of physiological

1. *New Scientist*, March 16, 1961, p. 699.
2. *Guardian*, Feb. 23, 1961, p. 3.
3. Macfarlane, R. G., Biggs, R. *M.R.C. Memor.* 1955, no. 32, p. 10.
4. Newlands, M. J., Wild, F. *Nature, Lond.* 1955, **176**, 885.

saline to give a milky suspension of approximately 10 mg. per ml. The capsule fragments are discarded, and the emulsion is stored at 4°C. It remains active for at least 3 months. Before use it is diluted 1 in 50; and it is substituted for the platelet suspension in the Biggs and Douglas technique.[3 5]

Specimen results obtained on a normal plasma were as follows:

	Clotting-time (sec.)	
Incubation-time (min.)	Suspension 10 mg. per ml.	Suspension 0·2 mg. per ml.
1	120	42
2	85	18
3	..	11
4	85	16
5	..	19
6	60	20

East Ham Memorial Hospital, London, E.7.

J. B. ENTICKNAP
T. S. LANSLEY.

ANOREXIA FOR ALCOHOL: A SIDE-EFFECT OF PHENETHYLBIGUANIDE

SIR,—During a trial of the oral antidiabetic drug phenethylbiguanide (' Phenformin ') in our clinic,[6] we have observed a curious side-effect—namely, loss of desire, or even repugnance, for alcoholic drinks, at least in some instances associated with a metallic alteration in their taste. This is by no means universal, and we do not know how common it is. Among more than two hundred diabetics who have been given phenethylbiguanide, we have inquired about it in fifty cases. These included seventeen total abstainers, and of the other thirty-three diabetics, who drank alcoholic beverages more or less regularly, ten showed this side-effect in various degrees.

In general the unpleasantness on drinking alcohol appeared during the first days of treatment, and with relatively low doses of phenethylbiguanide—e.g., 75–150 mg. daily. But it seems probable that, like the other side-effects, its frequency and intensity is roughly proportional to the dose. Usually this was the first side-effect to arise, and it was apparently independent of the others.

The following case-histories are typical:

CASE 1.—A man of 55, with " primary " diabetes of the fat adult, had been a chronic alcoholic for more than 10 years, taking about 3 litres of wine daily. He had frequent bouts of mild alcoholic poisoning. He was very interested in the trial of a new treatment for diabetes, recording carefully his diet and fractionated daily tests for glycosuria. This patient first drew our attention to the effect on alcohol, declaring spontaneously that he had observed during the first few days of treatment, even with the initial low dose of 75 mg. of phenethylbiguanide daily, such a dislike for alcoholic drinks that he had stopped them altogether. Other side-effects—namely, anorexia and postprandial satiety—only developed during the 3rd week. Without other anti-alcoholic treatment he remained totally abstinent for more than 3 months, but, having dropped the treatment, he resumed his former habits.

CASE 2.—A woman of 65, with primary diabetes, was a moderate and regular consumer of alcohol, without being addicted. From the beginning of treatment with phenethylbiguanide she lost her appetite, and noticed a vague alteration in the taste of wine. After 4 weeks this disappeared, but she then only drank sporadically, and even stopped having drinks at certain meals because of indifference.

CASE 3.—A healthy 27-year-old physician, who was unaware of this potential side-effect, tried the effect of taking phenethylbiguanide for a different purpose.[7] After a few days, when taking 75 mg. daily, he ordered a beer in a bar and sent it back because of a metallic taste, supposing it had deteriorated. Afterwards, when all alcoholic drinks he tried had the same metallic taste, he realised his error, and, having lost the desire, he stopped drinking alcohol. But about a week after the end of his 7-day trial of phenethylbiguanide, the desire for alcohol returned, and he resumed his usual moderate consumption of beer and wine.

In all clinical studies of phenethylbiguanide, anorexia for food in general has been the most common side-effect. Some workers [8 9] reported a metallic taste, but we think we are the first to draw attention to specific anorexia for alcoholic beverages. A subjective effect such as this can only be assessed by the double-blind technique, but the cases presented show that it exists. With further experience we suggest that this effect might be used therapeutically, not only for diabetics who are alcohol addicts but also for alcoholism in general, especially as it seems that healthy people are resistant to the hypoglycæmic effect of phenethylbiguanide.[10] At our suggestion, a trial has been started by psychiatrists at the Miguel Bombarda Hospital of Lisbon among alcohol addicts.

Associação Protectora dos Diabéticos Pobres, Lisbon, Portugal.

PEDRO EURICO LISBOA
NUNO CASTEL-BRANCO
MANUEL M. SÁ MARQUES.

5. Biggs, R., Douglas, A. S. *J. clin. Path.* 1953, **6**, 23.
6. Lisboa, P. E., Castel-Branco, N., Sá Marques, M. M., Arrobas, M. J., Cortez, M. T. *J. Méd. Lisboa*, 1959, **39**, 61.
7. Halpern, M. J., Lisboa, P. E. *J. Soc. Ciênc. Méd., Lisboa*, 1960, **124**, no. 9.
8. Pomeranze, J. *N.Y. St. J. Med.* 1958, **58**, 3824.
9. Weller, C., Macaulay, A. *J. Amer. geriat. Soc.* 1959, **7**, 128.
10. Fajans, S. S., Moorhouse, J. A., Doorenbos, H., Louis, L. H., Conn, J. W. *Diabetes*, 1960, **9**, 194.

Obituary

JOHN DOUGLAS ROBERTSON

M.D., D.Sc. St. And., Ph.D. Lond., F.R.C.P., F.R.I.C., D.P.H.

Dr. J. Douglas Robertson, consulting chemical pathologist to the West London Hospital, died on March 14 at the age of 57.

As a student at St. Andrews he combined a brilliant scholastic career with astonishing success playing for the university in rugby, association football, and cricket. In 1926 he graduated M.B. with distinction and two years later he came to London and began work at the Middlesex Hospital.

Here he joined the team that Sir Charles Dodds was assembling to inaugurate the new Courtauld Institute of Biochemistry. Though this was an institute of general biochemistry, special emphasis was placed on chemical pathology, and one section was given over entirely to the routine chemical work of the hospital. It was to this section that Robertson was to devote the next twenty years of his life. The introduction of insulin in 1923 had caused a great upsurge in chemical pathology as applied to medicine. New techniques of blood analysis were replacing the old and cumbersome methods of the previous decade and Robertson threw himself into this hive of activity with characteristic enthusiasm. Soon he became head of the clinical section of the institute. Of his work there E. C. D. writes:

" There is no doubt that the success of this department owed a very great deal to Robertson's energy and work. It expanded rapidly, and by the middle 1930s the standard and extent of biochemical investigation of clinical material was certainly equal to that anywhere in the world. Not only did he actively pursue routine work but he made many contributions to research.

" Fundamentally he was an observational scientist, and perhaps his greatest contribution lay in the thorough and sound investigation that he made on the determination of basal metabolic rate and its relation to the diagnosis and treatment of hyperthyroidism. Dissatisfied with the methods in use in this country in the early '30s he set about investigating the most economic way in which the basal metabolic rate could be deter-

mined accurately and reproduceably. He was able to show that this could be done on ambulatory patients and that there was no need for patients to be admitted to hospital for the test. Again, he was dissatisfied with the standards employed, since these were derived entirely from American sources. He made a survey of normal persons and, with D. D. Reid, made a set of standards which are now used by most workers in this country. But, though observation was his first choice, he was no mean experimentalist, conducting some elegant experiments on intraocular tension, on which he wrote a number of papers. His clinical investigations were of the highest degree of accuracy, and clinicians came to rely on his findings with absolute confidence.

"His versatility was astonishing. During this period of extremely hard work he kept his athletic interests. He played rugby football in London for the first years that he was there, and then gave this up for squash rackets of which he had had no previous experience. In a relatively short time he converted himself into a first-class player, and those who know the squash racket world need only be told that Robertson played regularly with Amr Pasha. In his younger days he was a lively and even boisterous companion, with a bizarre type of humour."

Soon after the war Robertson left the Courtauld Institute to become clinical pathologist at the London Clinic. After some years he resigned to take up his appointment at the West London Hospital. W. S. C. C. writes:

"Besides organising the routine activities and expansion of his department, he had a large private practice in clinical pathology. He also continued his research principally on hyperthyroidism and blood-sugar. During the last few years he co-operated with the department of rheumatology in several long-term investigations into the influence of corticotrophin and other steroids in the control of rheumatoid arthritis.

"He was a dynamic personality, and in spite of his lack of inches, noticeable in any gathering with his quick decisive talk and movements, his small imperial beard, and humorous sunburnt face. Although he was perhaps somewhat intellectually intolerant, his scrupulous honesty and fairness ensured him more friends than enemies, and he will be greatly missed by his colleagues at the West London."

JOSEPH MINTON
F.R.C.S.

Mr. Joseph Minton, ophthalmic surgeon to Hampstead General Hospital, the West End Hospital for Nervous Diseases, and Queen Elizabeth's Hospital for Children, Hackney, died at his home in London on March 12 at the age of 61.

Born in Lublin, Poland, he came to England in 1920 and qualified in 1926 from the Middlesex Hospital. While working as a single-handed general practitioner in Highbury, he became interested in diseases of the eyes, and from general practice he worked for and obtained his F.R.C.S. in 1932. After holding a clinical assistantship at the Royal Eye Hospital in London he gave up general practice and worked in his specialty as a house-surgeon, registrar, and research scholar at the Royal Eye Hospital. In 1936 he obtained his first consultant appointment at the Hampstead General Hospital. Others soon followed, and he eventually became consultant ophthalmic surgeon to Hampstead General Hospital, West End Hospital for Nervous Diseases, Queen Elizabeth's Hospital for Children, Hackney, and the London Jewish Hospital. During the late war he served as a major in the R.A.M.C. in the Baghdad military area and in the Ceylon Army Command. Besides his routine clinical work Mr. Minton was interested in industrial ophthalmology, and in 1947 he gave a Hunterian lecture at the Royal College of Surgeons on this subject. His book on *Occupational Eye Diseases and Injuries* was published in 1949, and he was lecturer in industrial ophthalmology at the Royal College of Nursing and the Royal Institute of Public Health and Hygiene. In latter years he had built up one of the best private collections of slides and photographs of eye diseases, and he always illustrated his lectures with many of these.

J. F. writes:

"Mr. Minton's skill and gentle manner, together with his great interest in patients as human beings with their personal and social problems in addition to their presenting eye conditions, earned him their gratitude both in the hospitals where he worked and also in his extensive private practice. He always went to considerable trouble and pains to help all who sought his advice. This advice was sought by many young graduates and students, as well as by his patients, because he was attached to the Royal Free Teaching Hospital group."

Mr. Minton leaves a widow, two daughters, and a son, who is also a doctor.

Diary of the Week

MARCH 26 TO APRIL 1

Monday, 27th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. W. S. Stiles: Directional Sensitivity of the Retina.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Odontology*. Mr. G. R. Seward: Safety Precautions in Dental Radiology.

MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice*. Dr. Samuel Oleesky: Unusual Problems in Hypertension.

Tuesday, 28th

ROYAL SOCIETY OF MEDICINE
8 P.M. *Medicine*. Prof. G. M. Wilson, Prof. D. W. Smithers, Dr. Eirian Williams: Isotopes in Medicine.

INSTITUTE OF CARDIOLOGY
5 P.M. (1, Wimpole Street, W.1.) Dr. Stanley J. Sarnoff (National Heart Institute, Bethesda): Reflex Regulation of the Transport Function of the Atrium. (St. Cyres lecture.)

ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) *Medical Section*. Mr. J. Hajnal: Cousin Marriages, Random Mating, and the Size of Isolates.

Wednesday, 29th

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. Telfer B. Reynolds (Los Angeles): Management of Acute Renal Failure.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. F. E. Camps: Domestic Coal Gas—Friend or Foe.

Thursday, 30th

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Dr. C. M. Fletcher: Problem of Observer Variation in Clinical Diagnosis.

Appointments

CHAMBERS, H. N., M.B. Lond., F.F.A. R.C.S.: part-time anæsthetist, Nottingham area.

DUNNILL, M. S., M.D. Brist., M.R.C.P.: consultant pathologist, Radcliffe Infirmary, Oxford.

RUSTAGE, J. H., M.B. Lpool, D.M.R.D.: consultant in radiology, Halifax/Huddersfield area.

SHEA, F. W., M.CH. Lpool, F.R.C.S.E.: consultant in orthopædic surgery, Leeds/Otley area.

East Anglian Regional Hospital Board:

COADY, T. J., M.B. Glasg.: medical registrar, Foxhall Hospital, Ipswich.

FLEMING, J. S., M.B. Edin., M.R.C.P., M.R.C.P.E.: medical registrar, Regional Cardiac Unit, Papworth Hospital.

GHOSHAL, T. K., M.B. Calcutta, D.O.M.S.: ophthalmic registrar, West Norfolk and King's Lynn General Hospital.

HELLEWELL, JOHN, M.B. Lond., D.A.: anæsthetic registrar, Ipswich and East Suffolk Hospital.

KANDELA, D., M.B. Baghdad: anæsthetic registrar, Newmarket General Hospital.

KIRKPATRICK, H. W., M.B. Cantab.: surgical registrar, Ipswich and East Suffolk Hospital.

MUSAHEB, E. A. G., M.B. Lucknow: medical registrar, Ipswich chest clinic and St. Helen's Hospital, Ipswich.

SAMANTA, S. K., M.B. Calcutta: orthopædic registrar, West Norfolk and King's Lynn General Hospital and St. James' Hospital, King's Lynn.

Colonial Appointments:

COMER, P. G., M.B. Wales: medical officer, Sarawak.

ROWLAND, H. A. K., D.M. Oxon., M.R.C.P., D.T.M. and H.: specialist physician, Sierra Leone.

RUGGLI, P. A., M.D.: resident surgeon, St. Lucia.

SCOTLAND, W. H. D., M.B. Glasg., M.R.C.O.G.: specialist (obstetrician and gynæcologist), Uganda.

WILSON, SARAH D., M.B. Belf., D.P.H.: M.O. (health), Jamaica.

Notes and News

TWIN SELVES

ADDRESSING a conference of local welfare authorities on March 15 Mr. Enoch Powell, the Minister of Health, described the local health authorities as their "twin selves". Indeed he was not sure whether even that expression did not understate the closeness of the relation between the health and welfare powers. He would prefer to hyphenate and talk about health-and-welfare authorities. There was really no intelligible boundary line between the services provided under the National Health Service Act and under the National Assistance Act. The division between the two was probably of partly historical, and partly accidental origin, and had little or no contemporary or logical significance. Some powers were actually duplicated. For instance residential accommodation which might be used for people with mild mental disorder could be provided under both Acts. But whatever the illogicalities of the statutory framework, the health-and-welfare services ought to be a single entity from the point of view of those whom they served. Turning to the importance of developing our community services, he said: "Between hospital and the outside world, the gulf, whatever we may do to narrow or bridge it, must always remain distinct and profound: it is the transition to a totally strange environment, with its own life and rules and rhythms. Always the hospital must be a law unto itself: it does not adapt itself to the individuals who pass through it. In the health and welfare services we are finding the secret more and more of handling people as individuals according to their own peculiar needs. This must, wherever it is possible, be right. When over the coming decades we together, the National Health Service and the local authorities, alter the pattern of hospital provision by the development of community care, we shall not only be bringing our organisation into accord with the best that the knowledge and practice of modern medicine have to offer; we shall also be realising a system which is better than that which exists today because it will be more human."

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University of Birmingham

At congregations to be held on July 14 and 15 the honorary degree of D.SC. will be conferred on Prof. A. F. Cournand, professor of medicine in the Columbia University College of Physicians and Surgeons, New York, and Prof. P. B. Medawar, Jodrell professor of zoology and comparative anatomy in University College, London, and of LL.D. on Mr. L. Farrer-Brown, director of the Nuffield Foundation, and Prof. J. M. Mackintosh, director of medical education and training, World Health Organisation.

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The 25 newly elected fellows of this society include:

Dr. L. H. GRAY, director of the British Empire Cancer Campaign research unit in radiobiology, Mount Vernon Hospital and Radium Institute, Northwood; Dr. MONTAGUE MAIZELS, professor of clinical pathology in the University of London at University College Hospital Medical School; Dr. A. A. MILES, director of The Lister Institute and professor of experimental pathology in the University of London; Dr. G. J. POPJAK, director of the Medical Research Council Experimental Radiopathology Research Unit, Hammersmith Hospital, London.

Association for the Study of Medical Education

Prof. John P. Hubbard will deliver a lecture on Thursday, April 20, at 5 P.M., at the Royal College of Physicians, Pall Mall East, London, S.W.1. He will speak on medical examining in the U.S.A.

International Cancer Congress

This congress, to be held under the auspices of the International Union Against Cancer, will take place from July 22 to 28, 1962, in Moscow. Further particulars may be had from the general secretary, Prof. L. Shabad, or the assistant general secretary, Dr. N. Perevodchickova, of the Soviet National Organising Committee, Academy of Medical Sciences of the U.S.S.R., 14, Solyanka, Moscow.

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The permanent section on biological standardisation of this Association is to hold an international congress from Aug. 28 to Sept. 1 in London. Further particulars may be had from the secretary of the congress, Central Veterinary Laboratory, Weybridge, Surrey.

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The Laboratory Animals Centre is to hold a symposium on this subject on Tuesday, May 30, at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2. Further particulars may be had from the secretary of the centre, M.R.C. Laboratories, Woodmansterne Road, Carshalton, Surrey.

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The annual general meeting of the members of the Auxiliary Royal Army Medical Corps Funds will be held on Monday, April 10, at 4.45 P.M., at 11, Chandos Street, London, W.1.

The consultant staff dinner of the Royal Northern Hospital, to which all previous members of both senior and junior medical staff are invited with their wives, will be held on Wednesday, April 19, at 8 P.M., at the Zoological Society of London, Regent's Park, N.W.1. Tickets (45s.) may be had from Dr. E. C. O. Jewesbury, Royal Northern Hospital, London, N.7.

CORRIGENDUM: We regret that last week the name of Mrs. F. Toole Stott, S.R.N., whose letter appeared on p. 620, was given incorrectly on our cover.

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